Dear Cancer Researcher:

This **SPECIAL LISTING** of Current Cancer Research Projects is a publication of the **INTERNATIONAL** CANCER RESEARCH DATA BANK (ICRDB) Program of the National Cancer Institute. Each **LISTING** contains descriptions of ongoing projects in one selected cancer research area. Approximately 50 different cancer research areas are covered by a separate **SPECIAL LISTING.**

The present series of **SPECIAL LISTINGS** is a third edition, and begins with number 201. This series will update the second edition which included **SPECIAL LISTINGS** numbered 101 through 147. Depending on the total number and types of cancer research summaries received, the third edition will have at least 47 titles, and possibly a few more. In most cases, each third edition **SPECIAL LISTING** will replace the exact subject area of a second edition **LISTING** (SL 201 replacing SL 101, etc.). Whenever the number and variety of summaries requires a change in this procedure, a notation will be made in the specific **LISTINGS** affected.

The purpose of these **LISTINGS** is to promote and facilitate the exchange of information among cancer scientists. The project descriptions in the **LISTINGS** are provided by cancer scientists from more than 50 different countries. Researchers are urged to prepare accurate summaries which will be rapidly processed for inclusion in the CANCERPROJ data base as well as future **SPECIAL LISTINGS.**

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NCI/ICRDB/SL-423
(Updates NCI/ICRDB/SL-323)

RESEARCH AREAS

	Abstract Number
I. ACUTE AND CHRONIC LEUKEMIAS	1
A. DIAGNOSIS AND PROGNOSIS	1
B. THERAPY OF LEUKEMIA IN CHILDREN	31
C. THERAPY OF LEUKEMIA IN ADULTS AND UNSPECIFIED AGE GROUPS	54
1. CHEMOTHERAPY OF ACUTE MYELOGENOUS AND ACUTE NONLYMPHOCYTIC LEUKEMIA	54
2. CHEMOTHERAPY OF ACUTE LYMPHOCYTIC AND ACUTE LYMPHOBLASTIC LEUKEMIA	77
3. CHEMOTHERAPY OF CHRONIC MYELOGENOUS, AND CHRONIC LYMPHOCYTIC LEUKEMIA	90
4. CHEMOTHERAPY OF ACUTE LEUKEMIAS AND LEUKEMIAS (UNSPECIFIED)	92
5. RADIOTHERAPY AND IMMUNOTHERAPY	113
6. OTHER AND NON-SPECIFIC THERAPY	124
D. PROTOCOLS	139
II. HODGKIN'S LYMPHOMA	154
A. DIAGNOSIS AND PROGNOSIS	154
B. RADIOTHERAPY	164
C. CHEMOTHERAPY AND IMMUNOTHERAPY	177
D. PROTOCOLS	198
III. NON-HODGKIN'S LYMPHOMAS	207
A. DIAGNOSIS AND PROGNOSIS	207
B. RADIOTHERAPY	221
C. CHEMOTHERAPY AND IMMUNOTHERAPY	225
D. PROTOCOLS	239
E. OTHER AND NON-SPECIFIC THERAPY	251
IV. SUPPORTIVE CARE OF LEUKEMIAS AND LYMPHOMAS	259
A. BONE MARROW TRANSPLANTATION OF ACUTE LEUKEMIA	259
B. BONE MARROW TRANSPLANTATION OF CHRONIC LEUKEMIA, UNSPECIFIED LEUKEMIA, AND LYMPHOMAS	273
C. PLASMAPHERESIS, LEUKAPHERESIS, AND TRANSFUSIONS	284
V. COOPERATIVE GROUPS	293
A. CANCER AND LEUKEMIA GROUP B (CALGB)	293
B. EASTERN, SOUTHEAST AND SOUTHWEST COOPERATIVE GROUPS (ECOG, SEOG AND SWOG)	319
C. CHILDREN'S CANCER STUDY GROUP (CCSG)	338
D. MYCOSIS FUNGOIDES GROUP AND OTHER GROUPS	347
VI. BROAD PROGRAMS	351
A. LYMPHOMA-LEUKEMIA AND LEUKEMIA PROGRAMS	351
B. LYMPHOMAS AND OTHER COMPREHENSIVE PROGRAMS	359

Investigator Index

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CURRENT CANCER RESEARCH

I. ACUTE AND CHRONIC LEUKEMIAS

A. DIAGNOSIS AND PROGNOSIS

1. FLOW-THROUGH CYTOPHOTOMETRY WITH THE CYTOFLUOROGRAF IN CANCER RESEARCH

Vincent, P. C., Gunz, F. W., Zbroja, R., Sydney Hospital, Clinical Haematology Unit, *Macquarie St., Sydney, N.S.W. 2000, Australia*

OBJECTIVE: To continue to evaluate applications to cancer research of flow-through impulse cytophotometry using the cytofluorograf, with particular reference to (a) attempted cell synchronization during induction therapy in patients with acute myeloblastic leukemia, (b) effects of chemotherapy on cell cycle characteristics in vitro and in vivo, (c) measurement of cell cycle parameters in solid tumors, (d) lymphocyte subpopulations in chronic lymphocytic leukemia and in lymphomas, (e) expansion of cooperative studies to include cytophotometric analyses of specimens submitted by other cancer research centres.

APPROACH: Serial bone marrow samples from patients with AML undergoing induction therapy will be analyzed to determine the distribution of cells within the proliferative cycle following initial treatment with hydroxyurea. Results will be available within 2 or 3 hours of the sample being taken and will be used to guide the timing of subsequent chemotherapy. Once the techniques are fully worked out in AML, similar studies will be undertaken in patients with other tumors receiving chemotherapy.

PROGRESS: Results to date show that the changes in cell cycle characteristics following chemotherapy vary considerably from patient to patient, emphasizing the need for individual studies in each subject. Some patients have shown evidence of synchronization of cell division, but it seems likely that cycle-independent reduction of tumor cell mass occurs in all patients and may be a more significant mechanism.

2. DIFFERENTIATION OF LEUKEMIA CELLS

Terada, M., Ministry of Health & Welfare, National Cancer Center, Section of Prevention of Carcinogenesis, *5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Tokyo, Japan*

OBJECTIVE: The long-term goal of the present investigation is to understand molecular mechanisms involved in blocks in differentiation of human leukemic cells, and to apply the information in treatment and diagnosis of various forms of human leukemia. The short-term purpose of the present studies is to clarify the biological roles of cellular glycoproteins in leukemic cells.

APPROACH: Human promyelocytic leukemia cells (HL-60) and Friend virus infected murine erythroleukemia cells (MELC) in culture are the experimental systems under investigation. HL-60 will be induced to differentiate mature myeloid cells by tunicamycin, which specifically blocks synthesis of glycoprotein by lipid-linked pathway. Glycoproteins before and after induction of differentiation will be analyzed by biochemical and immunological techniques. MELC can be induced to differentiate by various compounds, including nicotinamide and its related compounds, which inhibit poly(ADP-ribose) synthetase in vitro. With these compounds, as a tool, the significance of ADP-ribosylated protein will be analyzed in intact cells during the course of differentiation.

3. NEW TECHNOLOGY FOR CLASSIFYING HUMAN LEUKEMIA

Stang, H. D., Salser, W., Cline, M. J., Higuchi, R., Heindell, H., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

Traditionally, human leukemias have been diagnosed and classified by morphologic and histochemical techniques. Recently, introduction of specific enzyme analyses and cell surface antigens has refined the classification of acute lymphocytic leukemia. With the exception of morphologic subvariants such as monoblastic and promyelocytic leukemia, there has been little success in subclassifying the acute myeloid leukemias. We propose the application of recombinant DNA technology to construct a 'library' of gene sequences corresponding to different developmental stages of acute myeloid leukemia. The library will be constructed from freshly isolated leukemic cells and from two 'immortal' leukemic cell lines. The library will be used to classify human leukemias according to their expression of particular gene sequences. We will then make the appropriate correlation between such a classification and traditional morphology, histochemistry, response to treatment and the natural history of leukemia in a given patient. If any unique leukemia-related sequences are detected, these may serve as diagnostic probes for response to therapy and for relapsed disease.

4. FACILITATED DETECTION OF ACTIVE ACUTE MYELOGENOUS LEUKEMIA

Hanker, J. S., University of North Carolina, Chapel Hill Campus, Dental Research Center, *Chapel Hill, North Carolina*, 27514, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

5. HIGH DOSE METHOTREXATE PROJECT IN LEUKEMIA - DIAGNOSTIC AND THERAPEUTIC STUDIES

Moe, P. J., Nygaard, R., Dahl, T., University of Trondheim, Barneklinikken, *7000 Trondheim, Norway*

I. High dose methotrexate studies.

OBJECTIVE: Our program for treating children with ALL is not followed by all departments of pediatrics in Norway. Different types of biochemical studies are performed on samples from the children in order to classify the cases with respect to type of leukemia and to follow them with respect to activity of the disease.

APPROACH: All children with ALL are receiving a special leukemia treatment program. Clinical and hematological information is obtained on all cases. Lysozyme activity and ferritin concentration are determined before and during therapy of the children. We are also planning other types of studies in order to disclose early relapse, for instance CNS leukemia. Methotrexate determinations are performed in serum and spinal fluid during high dose methotrexate infusion. We are also planning to perform animal studies with tissue analyses of methotrexate.

PROGRESS: Several articles have already been published, among them 1) Pharmacokinetics of high dose methotrexate treatment of leukemia in children, Europ. J. Pharmacology 1978; 2) High dose methotrexate in acute childhood leukemia, Acta Paediatr. Scand., May 1978; 3) Serum lysozyme in children with acute leukemia, Europ. J. Pharmacol, 1978.

II. Childhood leukemia in the Nordic countries. This is an extensive epidemiologic study, involving registration of all long time survivors of acute leukemia in the five Nordic countries.

6. CHILDHOOD LEUKEMIA IN NORWAY 1963-1979

Moe, P. J., Johansen, O. J., Universitetet i Trondheim, Dept. of Paediatrics, *7000 Trondheim, Norway, Norway*

Information about all cases of childhood leukemia diagnosed in Norway during the period 1963-1979 has been collected by contacting hospitals, particularly all pediatric departments, and for the first years - all the departments of internal medicine as well. Information has also been obtained from the National Cancer Registry as cancer registration is compulsory in Norway. Information was obtained as to the type of leukemia, year of diagnosis and survival time. The first part of this study has already been published. The aim of the second part of this study is to register all current cases of childhood leukemia with emphasis on cell-type, treatment regimen, results of therapy, and possible sequelae of the use of intermediate dose levels of methotrexate for almost all cases of lymphocytic leukemia diagnosed in Norway after 1975.

7. ACUTE LYMPHOBLASTIC LEUKEMIA - AN IMMUNOLOGICAL STUDY OF A POSSIBLE T-CELL MALIGNANCY

Chechik, B. E., Mount Sinai Hospital, Research Department, *600 University Ave., Toronto, Ontario,* M5G 1X5, Canada

The application of T- and B-cell markers to the investigation of acute lymphoblastic leukemia (ALL) has resulted in an unmasking of the heterogeneity of the disease. One of these markers, human thymus/leukemia-associated antigen (HThy-L) has been studied, isolated, purified and characterized by the applicant in collaboration with Dr. E.W. Gelfand. Recently, we succeeded in developing a competitive radioimmunoassay for quantitation of HThy/L in cell extracts and plasma.

OBJECTIVE: This study was designed to define further the specificity of HThy-L and use this marker in investigations of pathways of T-cell differentiation in normal conditions and in leukemias.

APPROACH: Using a radioimmunoassay, we have demonstrated increased quantities of this antigen in leukemic cells and plasma from all patients with T-cell ALL and a considerable number of patients with other forms of acute leukemia. Neither healthy subjects nor patients with non-leukemic disease had increased quantities of HThy-L in peripheral blood mononuclear cells. The study of established hematopoietic cell lines has demonstrated that increased quantities of HThy-L are a more stable feature of leukemic T-cells than receptors for sheep erythrocytes (E). In this application, we propose to continue our studies on the clinical application of HThy-L, the relationship of the two forms of HThy-L with the pathway and stage of differentiation of normal and leukemic cells, and the biosynthesis and cellular localization of HThy-L and its structural characterization. The investigation of the acquisition of such cell markers at various stages of differentiation and of their role in differentiation may provide the means for diagnosing and monitoring ALL and for distinguishing or selecting more specific therapy for ALL of different origins.

8. FURTHER DEVELOPMENT OF A TEST WHICH DETECTS RESIDUAL DISEASE AND PREDICTS RELAPSE IN CHILDREN WITH ALL

Mott, M. G., Gentle, T., University of Bristol, Royal Hospital for Sick Children, Dept. of Child Health, *Bristol, England, United Kingdom*

OBJECTIVE: To determine whether it is possible to predict leukemic relapse by measuring peripheral blood lymphocyte blastogenesis induced by bone marrow blasts at subclinical levels.

APPROACH: A pilot study of co-cultivation of peripheral blood lymphocytes and bone marrow suggested that relapse could be predicted by measuring the stimulation ratio of the lymphocytes. The mechanism of this reaction and its verification in a larger series form the basis of this research study.

PROGRESS: This is a new project.

9. CELLULAR AND METABOLIC RESPONSES TO CORTICOSTEROIDS IN RELATION TO HUMAN LEUKEMIA

Bell, P. A., Sloman, J. C., University of Wales, Welsh National School of Medicine, Tenovus Inst. for Cancer Research, *34 Newport Rd., Cardiff CF1 1XP, Wales, United Kingdom*

OBJECTIVE: To analyze glucocorticoid receptor levels and in vitro responses of leukemic cells in relation to clinical response to glucocorticoid therapy and prognosis.

APPROACH: Leukemic cells are separated from peripheral blood or bone marrow. Glucocorticoid receptor levels in intact cells or cytosol are determined by incubation with saturating concentrations of 3H-triamcinolone acetonide. Effects on incorporation of 3H-thymidine or 3H-leucine are determined after exposure of cells to glucocorticoids for 24 hours in vitro. The data are correlated with morphological, cytochemical and membrane marker classifications and with clinical responses.

PROGRESS: All types of leukemic cells contain glucocorticoid receptors. In acute lymphoblastic leukemia (ALL) patients with null-ALL have higher receptor levels than patients with T-cell ALL. The cytosol assay gives false low values in myeloid leukemia due to receptor inactivation. No clear relation between in vitro metabolic responses and clinical responses to glucocorticoids has yet been established.

10. RELATIONSHIP BETWEEN SURFACE MARKERS AND CYTOCHEMICAL STAINS IN ALL

Donoso, J., Taboada, H., Grebe, G., Universidad Catolica de Chile, Depto. de Pediatria, *Casilla de Correo #89, Puente Alto, Chile*

OBJECTIVE: To determine the relationship between these two methods of classifying acute lymphatic leukemia in children, with emphasis on determining the relationship between subpopulations of T leukemias and acid phosphatase stain.

METHOD: Upon diagnosis, studies are performed on membrane receptors using the rosette formation test (T lymphocytes) and the synthesis of immunoglobulins (B lymphocytes), with which the leukemia is classifed into T-B-null.

Then studies are performed with cytochemical stains (PAS acid phosphatase), and clinical studies are performed (thoracic X-ray, etc.).

The evolution of the child is followed to observe the behavior of the various subgroups, with special focus on the 'null' acid phosphatase positive leukemias.

PROGRESS: This study has been underway for one year, during which time 35 children have been studied. It has been determined that 90% of the T leukemias are acid phosphatase positive. The significance of the other subgroups remains to be seen.

11. STUDY OF LEUKEMIA AND PRE-LEUKEMIC STATES USING BONE MARROW COLONY FORMATION AND CHROMOSOMAL BANDING

Waddell, C. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *2002 Holcombe Blvd., Houston, Texas,* 77031, United States of America

Bone marrow and peripheral blood colony formation was studied in patients with acute leukemias and chronic myeloproliferative disorders. Peripheral blood colony formation was markedly elevated in three patients with the diagnosis of chronic myelogenous leukemia, whereas it was normal in a patient with polycythemia rubra vera. Bone marrow colony formation in one patient with chronic myelogenous leukemia was markedly increased. Bone marrow colony formation in a patient with a hypercellular acute myelomonocytic leukemia was low, whereas another patient with 20% absolute marrow myeloblast percentage had low normal marrow colony formation but 13-fold increase in peripheral blood colony formation. An additional unusual patient had a severe peripheral blood pancytopenia and hypercellular oligoblastic marrow for one year, followed by a marked peripheral blood neutrophilic leukocytosis resembling chronic myelogenous leukemia, with a 25-fold increase in marrow colony formation and 250-fold increase in peripheral blood colony formation; however, no Philadelphia chromosome was present. One patient with acute lymphocytic leukemia, who was in peripheral blood and bone marrow remission, had significantly reduced bone marrow colony formation two months prior to bone marrow relapse. These studies will be continued with the goal of identifying patterns which may allow for prediction of response to therapy.

12. SUPPRESSOR CELLS IN THE PATHOGENESIS OF CHRONIC LYMPHOCYTIC LEUKEMIA

Hersey, P., Gunz, F. W., Kanematsu Memorial Inst., Immunology Unit, *Macquarie St., Sydney, N.S.W. 2000, Australia*

OBJECTIVE: To determine whether immunodeficiency in patients with chronic lymphatic leukemia may be due to overactivity of suppressor cells of the immune response.

APPROACH: The methods used in these studies were similar to those described by Moretta et al. (1977). B lymphocytes and T lymphocyes were separated from peripheral blood of CLL patients and age matched normal controls by sheep red cell (E) rosetting procedures similar to methods described previously (Hersey et al., 1975). The B lymphocytes of the normal controls were then mixed with varying numbers of normal T lymphocytes or CLL T lymphocytes and stimulated in culture for 6 days by the polyclonal B cell activator, pokeweed mitogen. Ig classes - IgG, IgM, and IgA - that have been synthesized in the cultures over this period were measured by nephelometric methods. Normal B lymphocytes received maximal 'help' by low numbers of T lymphocytes from normal subjects but were frequently unresponsive in the presence of T cells from CLL patients. To determine whether CLL T cells were deficient in 'help' or had excessive suppressor activity, they were added in varying numbers to cultures of normal B cells and T cells at optimal ratios for Ig production. Suppressor activity of the CLL T cells was then shown by the suppression of Ig synthesis from B cells in the presence of normal T cells. This culture system also allowed the function of CLL B lymphocyes to be tested by culturing them in the presence of normal T cells. The cell separation and culture procedures are now well established in our laboratory.

PROGRESS: Our results show that in patients with untreated CLL, immunoglobulin synthesis in vitro appeared to be suppressed by their T cells. In patients with more advanced CLL who had received various forms of treatment, abnormalities in both their 'helper' T cells and B lymphocytes could be detected. No correlation was found between cell division and' immunoglobulin synthesis in the cultures.

These results suggest that the underlying reason for immunodeficiency in CLL patients may change at different stages of the disease. (Text Abridged.)

BIBLIOGRAPHIC REFERENCES: Hersey, P., Edwards, A.E., and Edwards, J. Clin. Exp. Immunol., 23, 104, 1976. Moretta, L., Webb, S.R., Grossi, C.E., Lydyard, P.M., and Cooper, M.D. J. Exp., Med., 146, 184, 1977.

13. SPECIFICITY OF THE PHILADELPHIA CHROMOSOME TRANSLOCATION

Fraccaro, M., Pasquali, F., Casalone, R., Maraschio, P., Universita degli Studi di Pavia, Istituto Biologia e Genetica Medica, *C.P. 217, 27100 Pavia, Italy*

OBJECTIVE: The objective of this research is to define the specific event(s) leading to the formation of the Philadelphia chromosome in CML.

APPROACH: The approach was to screen a large number of Ph1-positive cases of CML to detect instances of unusual translocations resulting in the Philadelphia chromosome which might turn out to be informative. Among 240 Ph1-positive cases of CML we found six cases of Ph1 originated by a three-chromosome translocation. In these and other similar translocations reported in the literature no 'third' chromosome other than 9 and 22 seems to be preferentially involved. From these data it was inferred that the transposition of chromosome regions 9q34 and 22q11q to qter is essential for the development of CML.

PROGRESS: Collection of further data and extension of the analysis of the karyotypic variation found in CML in blastic phase are planned.

14. PROGNOSTIC FACTORS AND RESPONSES TO THERAPY IN CHRONIC MYELOID LEUKEMIA - EFFECT OF SPLENECTOMY

Baccarani, M., Lauria, F., Gugliotta, L., Zaccaria, A., St. Orsola's University Hospital, Division of Hematology, *40138 Bologna, Italy*

The present research program is based on the cooperation of 27 institutes covering most of Italy (Italian Cooperative Study Group on Chronic Myeloid Leukemia). The group has been actively working since 1973. Its general purposes are as follows: a) to standardize the methods of study and therapy of chronic myeloid leukemia (CML), b) to establish and develop prospective and controlled clinical trials for the therapy of CML. The specific purposes of this program are as follows: a) to evaluate the effect of early splenectomy in CML, b) to evaluate the effect of early administration and of cyclic administration of drugs commonly used for the therapy of acute leukemia, c) to identify and to analyze prognostic factors of CML in order to establish a classification of stages or strata at different risks of death. Such a classification should provide a basis for further therapeutic trials.

PROTOCOL CML/73 - The design of Protocol CML/73 was as follows: Initial and Continuation Chemotherapy - hydroxyurea during the first 2 years, and thereafter busulfan. Cyclic Chemotherapy - alternate courses (every 2 months) of arabinosyl cytosine (ARA-C) (70 mg/m2/12 h x 4 days) and of vincristine (1.4 mg/m2/week x 2 doses) plus prednisone (30 mg/m2/day x 15 days). Splenectomy - the operation was performed within 4 months of diagnosis in all patients under 60, in 11 hospitals. In the remaining hospitals, no patients were splenectomized. No. of Patients -139 (56 splenectomized), entered between March 1973 and October 1974.

The life-table analysis of this series of patients gives the following respective figures for surviving patients: time from diagnosis in years, percentage of splenectomized patients (n equals 56), percentage of non-splenectomized patients (n equals 83) - 1, 89.3, 89.1; 2, 83.9, 78.1; 3, 69.3, 64.7; 4, 56.6, 49.8; 5, 47.2, 37.9; 6, 26.9, 31.6.

Results suggest that splenectomy did not influence the course and duration of CML. In this trial, 42 patients are still alive. Further analysis will be devoted to complications, tolerance to chemotherapy and adverse effects, amount of therapy actually given and its relationship to survival. (Text Abridged.)

15. DIAGNOSIS AND THERAPY OF HORMONE SENSITIVE CANCER

Terenius, L., Simonsson, B., Uppsala Universitet, Biomedical Center, Dept. of Pharmacology, *Box 575, S75123 Uppsala, Sweden*

The heterogeneity in the clinical course of both chronic lymphocytic leukemia (CLL) and malignant lymphoma (ML) is well known. New tumor cell associated variables are needed for a better evaluation of disease progression, therapy effect and remission. In CLL we have found that subnormal IgA and IgG levels, high lymphocytic proliferative activity and a relatively low T cell number coincide with disease activity. A lower glucocorticoid receptor concentration was found in patients with inactive disease. The GR content in the peripheral lymphocytes was not correlated to the outcome of prednisolone therapy.

16. PROGNOSTIC FACTORS IN LEUKEMIA

Gahrton, G., Huddinge Sjukhus, Dept. of Medicine, *S14186 Huddinge, Sweden*

The objective of the project is to investigate certain parameters which may have prognostic value for patients with leukemia.

The approach in chronic myelocytic leukemia has been to study chromosomal aberrations before and during progression of the disease. The Q-banding technique has been used for chromosome analysis. The prognostic implications of variant translocations are studied in particular and, furthermore, the implication of new aberrations appearing during progression of the disease has been studied. The approach in acute leukemia has been similar. In chronic lymphocytic leukemia, polyclonal B-cell mitogens have been used to stimulate the cells. This new method has made it possible to study relevant karyotypic changes in this disease. Other approaches have been to study colony-stimulating activity of leukemic cells and colony-forming cells in the bone marrow and peripheral blood. Attempts have also been made to study the uptake of certain chemotherapeutic agents in leukemia cells before treatment. The quantitative uptake of the drug in leukemic cells in vitro has been correlated with the therapeutic efficacy of the drug. Such tests may be of importance in the future as predictive tests for chemotherapy.

17. EPIDEMIOLOGY OF MYELOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

Weiss, N. S., Daling, J. J., University of Washington, School of Public Health & Community Medicine, Dept. of Epidemiology, *4000 15th Ave. N.E., Seattle, Washington*, 98105, United States of America

This case-control study aims to identify and evaluate risk factors for multiple myeloma and chronic lymphocytic leukemia. Cases will be identified through population-based cancer registries in the states of Washington and Utah, and in Detroit and Atlanta, over a three-year period. Control subjects will be selected from the general populations in which the cancer cases occurred, using probability sampling methods such as area sampling and random digit dialing. Cases and controls will be interviewed with particular attention to variables related to chronic antigenic stimulations, e.g. past illnessses, allergies, drugs, etc. Detailed residence and occupational information will also be obtained in an attempt to generate new etiological hypotheses.

18. EPIDEMIOLOGIC AND HLA STUDY OF LEUKEMIA

Szklo, M., Humphrey, R., Bias, W., Linet, M., Johns Hopkins University, School of Hygiene & Public Health, Dept. of Epidemiology, *615 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

The major objective of this research is to study the postulated association between CLL and chronic antigenic stimulation (related to infections, inflammatory processes and autoimmune diseases) by means of medical chart review and interview in a case-control study. We are also exploring the postulated increased familial incidence of CLL and other lymphoproliferative malignancies. We are examining possible associations of CLL with occupation, smoking, alcohol use, immunizations and operative procedures involving the lymphoproliferative system (tonsillectomy, splenectomy, etc.) in order to develop additional etiologic hypotheses.

A medical record room search of all Baltimore SMSA hospitals is one of the prime sources for ascertaining cases. Physicians have reviewed 339 charts at 2 of the 3 major university hospitals and at 2 of the largest community hospitals where a large proportion of CLL cases are expected to have been seen. At present, this has yielded 121 cases diagnosed as CLL. Actually, 11/121 (9%) cases called CLL did not meet the criteria for CLL as established by the NCI CLL/Myeloma Task Force because of absolute lymphocyte counts less than 15,000/mm3. 28/121 (23%) of cases called CLL are probably cases of well-differentiated lymphocytic lymphoma.

Each case is matched with two controls with any malignancy other than a lymphoproliferative neoplasm and two controls with any non-malignant disease. The matching variables include age (within 5 years), sex, race, date of diagnostic admission and hospital of admission.

We have just begun the interview and blood-drawing portion of the study. We hope to identify differences in HLA types between patients with CLL and controls. We will then attempt to correlate these differences with epidemiologic and clinical characteristics of the various subgroups of our population of cases and controls.

19. MORPHOMETRIC ANALYSIS OF BONE MARROW BIOPSIES IN ACUTE LEUKEMIA

Steenbergen, J., Burghouts, J., Haanen, C., Wessels, J., Katholieke Universiteit Nijmegen, Dept. of Internal Medicine, *Erasmuslaan 4, Nijmegen, Netherlands*

OBJECTIVE: To obtain quantitative data about bone-marrow cellularity in leukemia patients, morphometric measurements at bone-marrow biopsies are performed before, during and after cytostatic therapy.

APPROACH: Biopsies, taken from the posterior iliac crest, are embedded in methyl-metacrylate. Sections are stained and microphotographed. The diapositives are projected on a suitable grid and the number of test points on the different cell types are counted as well as the number of test line intersections. From these data the cellularity as well as the ratios of the different cell types can be calculated.

PROGRESS: Biopsies from ten acute leukemia patients were embedded before, during and after therapy. All technical problems of morphometric analysis have been solved. Statistical analysis revealed the number of sections and the number of fields in each section that must be analyzed. At the end of 1978 morphometric analysis of patients' material started.

20. PROSPECTIVE CLINICAL, CYTOGENETIC AND MORPHOLOGIC STUDIES IN LEUKEMIA

Weinfeld, A., Ridell, B., Waldenstrom, J., Swolin, B., University of Goeteborg, Sahlgren's Hospital, Division of Oncological Hematology, Dept. of Medicine II, *41345 Goeteborg, Sweden*

Chronic granulocytic leukemia and refractory anemia or 'preleukemia' are prospectively studied from time of diagnosis until the development of blastic crisis or frank acute leukemia.

Special interest is focused on studies of cytogenetics and on the ultrastructure of megakaryopoiesis in relation to platelet kinetics. The development of chromosome abnormalities is pursued at medullary and extramedullary sites such as spleen, liver and lymph glands. Our results show that transformation of CGL often occurs at extramedullary sites. Attention is directed towards early diagnosis and treatment of metamorphosis in CGL.

Cytogenetic studies in 9 patients with the '5q- syndrome' are consecutively carried out during the course of their disease. These patients have a variable clinical picture, but all of them have a megakaryocytic dyscrasia. It is still to be shown whether the 5q-chromosome aberration is specific and whether it is of prognostic importance.

21. LEUKEMIA MONITORING BY FLOW CYTOMETRY/SORTING

Andreeff, M., Sloan Kettering Inst. for Cancer Research, Dept. of Pathology, *410 E. 68th St., New York, New York*, 10021, United States of America

The objective of the proposed study is to monitor a large number of acute leukemias of adults and children by flow cytometry/cell sorting techniques. These data, to be determined serially through all stages of disease, will provide a more precise means of evaluating treatment protocols and predicting relapse. Aneuploidy, present in more than 50% of the childhood and in 16% of the adult leukemias, will serve as a marker. Flow cytometric DNA-RNA measurements, also useful for the classification of leukemias, will determine the leukemic DNA stemline, and thus detect aneuploidy. Patients with aneuploidies will be followed serially during induction, consolidation and maintenance therapy and thereafter. Identification of very low numbers of aneuploid leukemic cells will be performed in three different ways: 1) multiparameter flow-cytometry measurements of more than 1 million mononuclear cells per sample (blood and bone marrow); 2) enrichment of leukemic cell populations by 1xG velocity sedimentation and flow-cytometry and 3) combined flow-cytometric cell sorting-autoradiographic techniques to distinguish hyperdiploid G1 leukemic cells from normal hematopoietic S cells. In addition, differences in chromatin structure of intact leukemic vs. normal hematopoietic cells, as determined by flow-cytometric measurements of acridine orange binding after acid and thermal denaturation, will be used to identify small number of diploid as well as aneuploid leukemic cells. These results will be compared with morphological/cytochemical findings by light microscopy and with special studies conducted in other laboratories.

22. CYTOLOGICAL STUDIES IN HUMAN LEUKEMIA

Trujillo, J. M., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Laboratory Medicine, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

During the last few years a series of chromosomal alterations associated with acute leukemia has been found, in our laboratory, to appear in a repetitive fashion in different and unrelated individuals. Initial investigations during this short period of time indicate that these aneuploid profiles may have a considerable clinical significance, particularly from a prognostic point of view. In addition, simultaneous ultrastructural studies of samples of hematopoietic tissue obtained from these patients have demonstrated a specific nuclear alteration in the majority of the patients carrying aneuploid clones. The present proposal intends to continue and expand these sequential cytological studies of the leukemic patients in order to better characterize the phenomenon of aneuploidy in human leukemia and to more precisely identify the chromosomal elements involved in these aberrations. The chromosomal changes will be analyzed in greater detail than heretofore by the application of new cytogenetic techniques (Quinacrine mustard fluorescence, Giemsa banding and heterochromatin staining). The true diagnostic and prognostic values of the aneuploid profiles that we have identified in acute leukemia will be determined. Other technical procedures, such as the use of colon-forming capacity, cytofluorometric determinants and euchromatin ultrastructural probe (Frenster's technique), will be utilized to evaluate the leukemic bone marrows. It is anticipated that this combined approach will provide fundamental information regarding the biological behavior of the leukemic cell population. Application of this knowledge to the care of the leukemic patient should result in an improved clinical management and a more individualized and rational form of therapy.

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23. NEGATIVE FEEDBACK REGULATION OF GRANULOPOIESIS BY LACTOFERRIN DURING LEUKEMIA AND MYELODYSPLASIA

Broxmeyer, H. E., DeSousa, M., Nishiya, N., Meyers, P. A., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

The capacity to assay hematopoietic committed stem cells in humans and factors which regulate their growth allows us to investigate normal and abnormal hematopoiesis in vitro and in vivo. We believe that defects in negative feedback regulation of granulocytic-monocytic stem cells are important in the development and progression of acute and chronic leukemia and myelodysplasia. We propose to use in vitro and in vivo approaches to study in depth a cell-free inhibitory activity we have recently reported and which we have now identified as lactoferrin. Lactoferrin is a well-characterized iron-binding glycoprotein which is presently available in purified form. Defects in the lactoferrin negative feedback regulation of granulopoiesis are probably involved in the pathogenesis and progression of leukemia and myelodysplasia.

The prognostic and diagnostic potential of these regulatory interactions will be explored. Large numbers of patients will be screened for the quantity and qualitative effectiveness of lactoferrin and for the response of normal cells and cells of patients to lactoferrin. This may allow us to detect residual leukemic cells during remission and may be a sensitive means to detect acceleration to the terminal phases of acute leukemia.

Normal and leukemic mice will be used to determine the in vivo action and significance of lactoferrin with regard to disease progression. Biophysical and immunological cell-separation procedures will be used to further elucidate the subpopulations of cells elaborating and responding to lactoferrin. A knowledge of the exact regulatory mechanisms and their lesions during disease will allow us to develop methods in an attempt to counteract the 'pathological' interactions and enhance physiological mechanisms in vitro and in vivo.

24. TERMINAL TRANSFERASE AS A BIOLOGICAL MARKER FOR HUMAN LEUKEMIAS

Tsiapalis, C. M., Papamichael, M., Hellenic Anticancer Inst., Dept. of Biochemistry/Immunology, *171 Alexandra Ave., Athens 603, Greece*

OBJECTIVE: Develop and adapt biochemical and immunological methods to measure terminal transferase in human leukemias. Such measurements may become useful in prognosis, diagnosis and during treatment and in remission of leukemic patients.

APPROACH: Determination of terminal transferase activity in the peripheral blood leukocytes and/or bone marrow of such patients.

25. STUDIES ON BIOCHEMICAL MARKERS IN HUMAN BREAST CANCER, LEUKEMIA AND LYMPHOMA

Skoog, L., Karolinska Sjukhuset, Dept. of Tumor Pathology, *S10401 Stockholm, Sweden*

OBJECTIVE: To evaluate the use of biochemical markers in subdividing human tumors with respect to malignancy.

APPROACH: Four enzyme markers (TdT, adenosinedeaminase, 5' nucleotidase and hexosaminidase) and cytosol glucocorticoid receptor levels are measured in the lymphoma-leukemia group. The breast cancer studies include determination of estrogen receptor levels and plasma membrane composition.

26. PURCHASE AND INITIAL OPERATION OF FLUORESCENCE ACTIVATED CELL SORTER FOR VARIOUS CANCER-RELATED STUDIES

Clark, A. M., Bradley, J., Burgoyne, Cant, Cox, Morley, Murray, Keighley, Finlay Jones, Martin, Zola, H., Flinders University of South Australia, Flinders University Cancer Research Unit, *Bedford Park, S.A. 5042, Australia*

The Cancer Research Unit of the Flinders University of South Australia is purchasing a fluorescence activated cell sorter for use in cancer-related studies by research workers in South Australia. The instrument has yet to be installed but a number of research projects are awaiting the arrival of the instrument. The sorter will be used by workers using animal tumor models to analyze the cellular composition of tumors and to prepare purified subpopulations of lymphocytes in order to further analyze their function in the immunological response to cancer. Studies using human malignant cells will be of two general types. Some studies will deal with the analysis of the nucleic acid content of cells which reflects their cell cycle antibodies. It is anticipated that some of these studies will lead to improved diagnostic examination of leukemic cells and samples from patients in remission to detect residual disease and to make an early diagnosis of relapse.

27. EARLY DETECTION AND MONITORING OF LEUKEMIA AND TUMORS IN CHILDREN AND ADULTS

Muller, H., Stalder, G., University Children's Hospital, Dept. of Genetics, *Romergasse 8, CH4005 Basel, Switzerland*

OBJECTIVES: 1) Recording of preleukemic states, i.e., hematological disorders highly conducive to leukemia. 2) Early detection of malignant lymphoma in children and adults. 3) Recording of mutagenic effects of the cytostatic therapy. 4) Cytogenetic characterization of solid tumor cells.

APPROACH: Chromosomally abnormal cells - suspected to be malignant - are to be detected and recorded by a systematic cytogenetic analysis of the tissue in question. For the chromosome analysis new staining techniques are used. Great effort is being made to investigate the cell population within a tumor supposed to be the subject of malignant transformation by using adequate techniques of cell isolation and cell culture. With relevant cytogenetic techniques defects of DNA repair mechanisms in aplastic anemia are visualized. For this purpose the cultured cells of the patient are exposed to specific aberration-inducing chemicals. After successful tumor therapy, chromosome defects and aberrations in the DNA content of sperms and somatic cells are being searched for.

PROGRESS: Every year some 150-200 new patients belonging to one of the above mentioned groups can be included in the study. The findings obtained contributed to the understanding of the significance of the chromosomal aberrations in the neoplastic process. A moderate but constantly increased frequency of spontaneous sister chromatid exchanges, indicating alterations on the DNA level, was found in a group of young patients suffering from aplastic anemia. DNA repair defects were primarily found in patients with anemia of the Fanconi type. As a rule the successful cytostatic treatment induced no persisting mutations on the light microscopical level of chromosome aberrations. Several prelimary reports about the different topics have been published.

28. LONG-TERM FOLLOW-UP OF CHILDHOOD CANCER SURVIVORS

Draper, G. J., Harnden, D. G., Heasman, M. A., Marsden, H. B., University of Oxford, Childhood Cancer Research Group, *S. Parks Rd., Oxford OX2 6HE, England, United Kingdom*

OBJECTIVES: The proportion of children with cancer and leukemia who are successfully treated has increased considerably during the past 15 years, but little is known about the long-term prognosis for such patients or their children. The primary objectives of this study are to investigate: (a) The incidence of second primary tumors and (b) the outcome of pregnancies among the survivors and the incidence of congenital defects and neoplasms among their children. The occurrence of such late effects will be analyzed in relation to the original tumor type and to the radiotherapy and chemotherapy used in treatment. Subsidiary objectives are to investigate continuing morbidity and the general 'quality of life' among survivors, and to determine the incidence and causes of late deaths.

It is proposed also to conduct chromosome studies, to establish a pathology registry for double primary tumors and possibly to perform detailed clinical examinations of some groups of patients.

APPROACH: The Childhood Cancer Research Group is coordinating a collaborative study which will include most of the survivors of childhood cancer treated in Britain from 1954 onwards and also many from earlier years.

Cases have been identified through cancer registries and certain major treatment centers. Further information on second tumors and late deaths will be obtained through hospitals and national record systems. Information on the subsequent health of survivors, their pregnancy histories and the occurrence of neoplasms and congenital defects in their offspring will be obtained by questionnaire studies through consultants and general practitioners.

For children treated in Scotland, subsequent hospital admissions, school health records and other medical records are being studied and compared with corresponding records for a sample of controls, using record linkage.

29. PEDIATRIC HEMATOPOIETIC MALIGNANCIES - PROGNOSTIC FACTORS IN CHILDHOOD LEUKEMIA

Murphy, M. L., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

30. CELLULAR FOLATE METABOLISM IN PRE-LEUKEMIA

Branda, R. F., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Medicine, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

Preleukemic states, such as aplastic anemia, sideroblastic anemia, erythremic myelosis and the 'preleukemic syndrome' often demonstrate morphologic and kinetic features of folate deficiency, and occasional patients with these diseases improve with empiric trials of folic acid. Recently we began investigating one such patient, a young man with severe aplastic anemia, who has a strong family history of leukemia, neutropenia and refractory anemia. Preliminary studies suggest that this patient and other family members manifest a previously undescribed defect of cellular folate uptake. Therapy with high dose folate resulted in marked clinical improvement of the aplasia. We suggest that similar defects of folate metabolism may cause hematologic abnormalities in other patients with preleukemic states and possibly contribute to leukemogenesis by altering nucleic acid metabolism. We propose to delineate more clearly the processes involved in the uptake and utilization of folate by normal human lymphocytes, bone marrow cells and red cells, and develop criteria and techniques for the identification of disorders of these processes. Using these techniques, patients with preleukemic states will be screened for evidence of impaired folate metabolism, and identified patients will be studied in detail to characterize their cellular abnormality. These patients will then be treated with high doses of folic acid and their clinical response measured. An attempt will be made to assess whether this treatment alters the risk of subsequent leukemic transformation in these patients with preleukemic states.

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B. THERAPY OF LEUKEMIA IN CHILDREN

31. CLINICAL PROTOCOL (PHASE II) OF REMISSION INDUCTION IN CHILDHOOD ACUTE MYELOBLASTIC LEUKAEMIA (AML)

Ekert, H., Waters, K. D., Royal Children's Hospital Research Foundation, Dept. of Hematology, *Flemington Rd., Melbourne, Victoria 3052, Australia*

HISTOLOGIC TYPE AND CLINICAL STAGE: All children with morphologic and cytochemical evidence of AML.

TREATMENT MODALITIES AND AGENTS: Cytosine arabinoside 10 mg/kg is infused over 24 hours. This is followed immediately by daunorubicin 45 mg/m2 and 24 hours later by adriamycin 45 mg/m2. A second course is repeated in 2 weeks. Bone marrow aspiration is used to test remission. All patients continue with cytosine arabinoside and 6-thioguanine for 3 courses at 5 day intervals followed by 5 days of oral cyclophosphamide and 2 further injections of adriamycin 45 mg/m2. Remission is maintained with cytosine and 6-thioguanine and intermittent BCG (Heaf gun inoculation) and allogenic AML cells injected intradermally.

PROTOCOL: Not controlled or randomized.

PRESENT STATUS: 20 entered. 66% C.R.

32. ACUTE NONLYMPHOCYTIC LEUKEMIA IN CHILDREN

Dahl, G. V., St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

33. PROTOCOL TMC-1 FOR NON-T ALL IN CHILDREN (AGED 2-14 YEARS)

Shetty, P. A., Antia, P. K., Damle, S. R., Nadkarni, J. S., Nadkarni, K. S., Tata Memorial Hospital, Dept. of Chemotherapy, *Dr. Ernest Borges Marg, Parel, Bombay 400012, Maharashtra, India*

OBJECTIVE: The study is planned to evaluate the importance of reinforcement therapy (same as induction therapy), given once in 3 months, in overall relapse-free survival.

APPROACH: The induction phase and sanctuary phase of treatment are similar for all patients. When the patients reach maintenance phase, they are randomized into two arms: (1) Reinforcement therapy plus maintenance and 2) maintenance therapy alone.

PROGRESS: So far 10 patients have been entered into arm 1 and 7 patients into arm 2. The median duration of follow-up is 6 months. No definite conclusions have been drawn.

34. CHEMOIMMUNOTHERAPY (BCG) CONTROLLED TRIAL IN ACUTE LYMPHOCYTIC LEUKEMIA OF CHILDHOOD

Rice, M. S., Leahy, M. A., Toogood, I. R., Adelaide Children's Hospital, *72 King William St., Adelaide, S. Australia 5066, Australia*

OBJECTIVES: 1. To investigate whether intermittent chemotherapy, combined with immunotherapy, prolongs the duration of the first complete remission, compared with intermittent chemotherapy alone. 2. To investigate whether intermittent chemotherapy, combined with immunotherapy, results in longer survival than intermittent chemotherapy alone. 3. To determine the effects of these regimens on immunological function and on the incidence of infective and other complications.

APPROACH: A cooperative study (Australian Cancer Society Childhood Leukemia Study Group) using a standard protocol. Chairman of Study Group is Dr. H. Ekert, Royal Children's Hospital, Parkville, Victoria, 3052.

35. CONTROLLED CLINICAL TRIAL (PHASE III) OF CHEMOIMMUNOTHERAPY IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA (ALL)

Ekert, H., Jose, D. G., Tauro, G. P., Waters, K. D., Matthews, R. N., Matthews, J., Royal Children's Hospital, Clinical Haemotol. & Oncology, *Flemington Rd., Parkville, Victoria 3052, Australia*

OBJECTIVES: 1) Compare duration of first complete remission maintained with intermittent chemotherapy and BCG compared with intermittent chemotherapy only. 2) Determine the effects of these regimens on immunologic function and infective complications.

HISTOLOGICAL TYPE AND CLINICAL STAGE: Children with morphologic and cytochemical diagnosis of ALL are stratified on the basis of age, organomegaly and total white cell count into good prognosis (WCC 5-1000), average prognosis (WCC 10-30,000) and intensive therapy (WCC 30,000) groups.

TREATMENT MODALITY AND PROTOCOL OUTLINE: Good and average prognosis induced with vincristine and prednisolone, but cytosine and asparaginase are added in average prognosis groups. Intensive therapy group induced with cytosine cyclophosphamide and asparaginase. All children given prophylactic skull irradiation (2400r) and 4 injections of intrathecal methotrexate. Remission is confirmed by bone marrow aspiration. All patients are then randomized into either group A - 6 weeks of chemotherapy consisting of 6MP daily, weekly methotrexate and monthly vincristine followed by 2 weeks of no treatment; or group - some chemotherapy but one week after its cessation 0.25ml of BCG is inoculated with a Heaf gun. (BCG Commonwealth Serum Laboratory Pasteur strain protein content 75mg/ml viable organisms 6-20 x 10 to the 6th power/mg).

PRESENT STATUS: Ninety-seven randomized with at least 3/12 of follow up; 52 pending analysis. 63% C.R. at 152 weeks. No significant difference in BCG arm (48 patients) vs. no BCG arm (49 patients).

36. L-ASPARAGINASE IN REMISSION INDUCTION OF ALL IN CHILDHOOD

Wehinger, H., Kinderklinik am Stadtkrankenhaus, *Moencheberg-strasse 41, 3500 Kassel, Hessen, Federal Republic of Germany*

OBJECTIVE: To see if L-asparaginase is useful in remission induction of ALL as a third drug in addition to vincristine and prednisone when given at an interval after vincristine. (With simultaneous application there might be negative interference between L-Asp and VCR, because L-Asp arrests cells in the late S-phase, thus preventing the cells from proceeding to M to become vulnerable by VCR).

APPROACH: Thirty patients were randomized to receive either VCR plus Pred or VCR plus Pred plus L-Asp as an induction regimen for ALL in children. Asparaginase was given 24 hours after vincristine once weekly in a single infusion dose of 1000 U/kg. Meningosis prophylaxis and maintenance were performed the same way in both groups.

PROGRESS: After an observation time of 12-45 (mean 30) months no difference is seen between the two groups.

37. FREIBURG COOPERATIVE LEUKEMIA STUDY (1975)

Wehinger, H., Kinderklinik am Stadtkrankenhaus, *Moencheberg-strasse 41, 3500 Kassel, Hessen, Federal Republic of Germany*

OBJECTIVES: To find an optimal two-drug regimen for maintenance in childhood ALL.

APPROACH: This is a cooperative study of several German pediatric departments. Children with ALL who have been successfully brought into remission with vincristine and prednisone are subjected to meningosis prophylaxis, and then randomized to receive: a) 6-MP p.o. daily plus MTX p.o. once weekly; b) 6-MP p.o. daily plus MTX i.v. once every two weeks; or c) 6-MP p.o. daily plus MTX i.v. once every two weeks x4 followed by 6-MP p.o. daily plus Cyclo i.v. once every two weeks x4. The MTX course and the Cyclo course will alternate successively.

PROGRESS: We are still at the stage of patient accumulation.

38. HIGH DOSE METHOTREXATE PROJECT IN LEUKEMIA - DIAGNOSTIC AND THERAPEUTIC STUDIES

Moe, P. J., Nygaard, R., Dahl, T., University of Trondheim, Barneklinikken, *7000 Trondheim, Norway*

The summary for this project is under entry no. 5.

39. CHILDHOOD LEUKEMIA IN NORWAY 1963-1979

Moe, P. J., Johansen, O. J., Universitetet i Trondheim, Dept. of Paediatrics, *7000 Trondheim, Norway, Norway*

The summary for this project is under entry no. 6.

40. NEUROPSYCHOLOGICAL EFFECTS OF LEUKEMIA AND ITS TREATMENT

Goff, J. R., Marten, G. W., Powazek, M., Chien, L., George, S., Aur, R. J., Anderson, H. R., St. Jude Children's Research Hospital, Dept. of Psychiatry/Psychology/Social Services, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

The proposed study will investigate the neuropsychological status of children treated for acute lymphoblastic leukemia (ALL) in a longitudinal fashion by means of serial neuropsychological, audiological, and electroencephalographic examinations and by comparison with control groups consisting of siblings of leukemic children and comparably aged children with Wilms' tumor. All children admitted to St. Jude Children's Research Hospital for treatment of ALL between the ages of four and twelve (40-50 per year) will be serially evaluated for five years by means of the Reitan-Indiana Neuropsychological Test Battery for Children or the Halstead Neuropsychological Test Battery for Children as well as electroencephalograms and the Staggered Spondeic Word Test. Identical procedures will be administered to the control groups. If alterations in neuropsychological functioning do occur, they are expected to be variable across age groups, consistent within age groups. A thorough statistical analysis of the data will result in the detection of areas of neuropsychological dysfunction and determination of the etiology of any dysfunctions which occur. The determination of specific areas of neuropsychological dysfunction will facilitate the development of remediation strategies applicable to the classroom. Academic achievement will be monitored yearly to assess the effectiveness of any remediation initiated. By thoroughly examining a population at risk of CNS dysfunction during the high risk period, new knowledge can be obtained not only concerning the population of ALL children but also of the developing CNS in general.

41. ENVIRONMENTAL EXPOSURES AND CHILDHOOD LEUKEMIA

Pendergrass, T. W., Children's Orthopedic Hospital & Medical Center, Division of Hematology & Oncology, *4800 Sand Point Way N.E., Box C-5371, Seattle, Washington*, 98105, United States of America

Little is known of the role of parental occupational exposures or perinatal drug ingestion in the subsequent development of childhood acute lymphocytic leukemia. This study has two goals: a) development of a method for obtaining information on parental occupational and perinatal drug exposures, and b) testing of this method on parents of children diagnosed as having acute lymphocytic leukemia, between 1972 and 1979 in the state of Washington. Cases have been identified in the three major hospitals treating children with cancer in the State. For each case a hospital control has been selected to attempt to control for any differences in recall between parents of ill and presumably well children. General population controls will be obtained by use of a random digit dialing method. To date, 80% of case parents have been interviewed. Occupational data include a detailed review of occupational history and review of each job-related exposure. A detailed review of perinatal drug ingestion is obtained.

42. THERAPY-INDUCED GROWTH DISORDERS IN CHILDHOOD CANCER

Duck, S. C., Camitta, B. M., Klitgaard, H., Drucker, W. D., Hagen, T. C., Guansing, A. R., Medical College of Wisconsin, School of Medicine, Dept. of Pediatrics, *561 N. 15th St., Milwaukee, Wisconsin*, 53233, United States of America

Acute lymphocytic leukemia (ALL) is the most common malignancy of childhood. Currently about 50% of children diagnosed as having ALL will survive for 5 or more years. With improved survival times, many serious adverse effects of cancer therapy are being manifested: some of these are leucoencephalopathy, disrupted growth and development and neuroendocrine dysfunction. At present it is uncertain whether one can predict which children will experience these particular adverse effects and what if anything can be done to prevent expression of hormone dysfunction. The specific objectives are: 1. To establish if at any stage of therapy for ALL, there is an impairment of the neuroendocrine-endocrine end-organ axis, and to what extent such impairment is exposed clinically by disturbed growth and development. 2. To establish the relative 'necessity' and 'potential benefit' of appropriately timed trials of exogenous hormone therapy based on the temporal characteristics of these endocrine disruptions. Methods will involve a four-year prospective evaluation of newly diagnosed children with ALL. The new patients will be enrolled during the first 2 years of the study, allowing 2-3 year follow-up for the survivors. Each patient will be evaluated by extensive, sequential anthropometric parameters, bone age analyses, and basal and 'stress'-released hormone levels, measured at each phase of cancer therapy.

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43. CHEMOTHERAPY OF CHILDHOOD LEUKEMIA AND SOLID TUMORS - ACUTE LYMPHOBLASTIC LEUKEMIA

Kung, F. H., University of California, San Diego Campus, School of Medicine, Dept. of Medicine, *P.O. Box 109, La Jolla, California*, 92093, United States of America

This is part of a broader project. A summary of this subproject is not available.

44. BONE MARROW TRANSPLANTATION IN CHILDREN WITH LEUKEMIA

Dooren, L. J., Vossen, J. M., Rothbarth, P. H., deKoning, J., Kamphuis, R. P., Academisch Ziekenhuis Leyden, Dept. of Pediatrics, *Rijnsburgerweg 10, 2333 AA Leyden, Netherlands*

OBJECTIVE: Treatment of children with acute leukemia with poor prognosis in first remission by transplantation of bone marrow cells from MHC identical sibling donors as compared with conventional cytostatic therapy.

APPROACH: 1. Selection of treatment group for high risk leukemia patients. 2. Optimization of cell reductive and transplantation treatment. 3. Prevention and treatment of complications; optimalization of supportive treatment, including psychosocial guidance. 4. Longitudinal follow-up of several aspects of humoral and cellular immune capacities following bone marrow transplantation.

PROGRESS: Project will start approximately September 1, 1979.

45. SYNTHESIS AND PRE-CLINICAL TESTING OF THIOLATED POLYCYTIDYLIC ACID (MPC)

Henderson, E. S., Roswell Park Memorial Inst., Division of Medical Oncology, *666 Elm St., Buffalo, New York,* 14263, United States of America

This proposal is: 1) For the preparation of amounts of thiolated polycytidylic acid (MPC), a new compound with antitumor activity, of clinical grade purity, and sterility sufficient for adequate pre-clinical toxicological workup and for Phase I clinical trial, and 2) For the performance of preclinical toxicological evaluation of this compound. MPC has been shown to inhibit in vitro DNA polymerases, including reverse transcriptase isolated from human malignant cells, and to induce complete remissions in a limited number of children with acute leukemia. It has not yet been tested in the U.S.A.

The synthesis of MPC was developed by T.J. Bardos, M.D., the co-investigator of this grant proposal. All facilities and expertise required for the synthesis, preclinical testing, and clinical trial of MPC exist in Buffalo (SUNY at Buffalo and Roswell Park). The project is held up at present solely because of the large cost of starting material (polycytidylic acid) required for the synthesis of MPC. This grant is to request necessary funds for this starting compound.

46. DRUG EFFECT IN ACUTE LEUKEMIA

Lampkin, B. C., Wong, K. Y., Evert, C. F., University of Cincinnati, Children's Hospital Medical Center, Hematology Oncology Division, *Elland & Bethesda Aves., Cincinnati, Ohio,* 45229, United States of America

Excellent agreement in the percentage of cells in the S phase as determined by the labeling index and DNA histogram using the cytofluorograph 4802A was found in a majority of samples of marrow from children with acute leukemia. However, in a minority of cases there were gross differences. Interpretations of DNA histograms have been compared using the Fried method and probability paper. Thus far our data seems to be better interpreted using probability paper. The in vivo effect of dianhydrogalactitol (DAG) and VM26 singly on the cell cycle has been evaluated in 10 children (6 with acute leukemia and 4 with advanced solid tumors).

Inhibition of DNA synthesis occurred in both normal and leukemic cells after DAG and a G2 block was also seen in two leukemic patients. In each case there was a block in G2 after VM26.

The Robinson and Pike and Dicke, Spitzer et al. methods for evaluating marrow proliferation were evaluated on samples of cord blood, normal bone marrow and leukemic marrow (ALL, AML and CML). Our data confirms the results previously found using these methods of culture of marrow. Both methods were helpful in following the response to therapy of 5 children followed serially with CML. Interestingly, blasts grew also from cord blood.

Lastly, leukemic cells from a patient with acute undifferentiated leukemia have been growing in continuous culture for one year. These cells are EB virus negative and recently have grown in nude mice.

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47. COMBINED EFFECTS OF RADIATION AND CYTOTOXIC DRUGS ON THE RADIATION TOLERANCE OF THE CENTRAL NERVOUS SYSTEM

Hopewell, J. W., Karbal, A., University of Oxford, Research Inst., *c/o Churchill Hospital, Oxford, England, United Kingdom*

OBJECTIVE: Chemotherapeutic agents, in particular methotrexate, are currently being used in conjunction with brain irradiation as part of the prophylactic treatment of children with leukemia. It is proposed to examine the possible effects of various drug combinations on the radiation tolerance of the central nervous system.

APPROACH: It is proposed to investigate the mechanisms responsible for the development of damage in the brain and spinal cord in experimental animals. Effects will be evaluated by the quantitative assessment of cellular changes in histological material obtained by the serial killing of treated animals. The importance of field size will be investigated.

Modifications in normal tissue and tolerance produced by radiation of the spinal cord in combination with various dose levels of intrathecal methotrexate and other drugs will be determined by establishing the proportion of animals developing paralysis after 6 months. Iso-effect doses will be compared to determine the relative changes in cord tolerance.

In the brain, radiation depletion of the cells in the subependymal plate region will be used as a measure of radiation effects. Modifications in this response, produced by drug combinations, will be evaluated.

48. BCG VACCINATION AND LEUKEMIA

Katz, L., Steinitz, R., Israel Center for Registration of Cancer & Allied Diseases, *18-20 King David St., Jerusalem, Israel*

The possibility that the reported non-specific immunity conferred by BCG may have some influence in the prevention of leukemia in children is being investigated. In Israel a unique opportunity presents itself for studying the incidence of leukemia in BCG vaccinated children and in a non-vaccinated control group: since 1955 routine BCG vaccination of newborns has been carried out in all maternity wards in Israel - with the exception of the Jerusalem hospitals, where it was never introduced. The incidence of leukemia in children born in Israel since 1955, diagnosed after 1960 (the year the Israel Cancer Registry was founded) and up to the age of ten will be studied. Two hundred and sixty-three cases of leukemia in children have been identified. Their places of birth are now being ascertained.

49. EFFECTS OF CNS TREATMENT ON INTELLECTUAL FUNCTIONING OF CHILDREN WITH LEUKEMIA

Moss, H. A., Poplack, D. G., Hubbard, V. S., Siegel, S., Kellerman, J., U.S. Dept. of Health & Human Services, Public Health Service, Alcohol, Drug Abuse & Mental Health Admin., National Inst. of Mental Health, Developmental Psychology Laboratory, *Bethesda, Maryland,* 20014, United States of America

The effects of CNS treatment (cranial irradiation and intrathecal chemotherapy) on the cognitive and perceptual functioning of children with leukemia are investigated. One study compared a group of leukemic children in remission with a matched group of sibs. Comparisons were based on results from a battery of psychological tests (Wechsler, Bender-Gestalt and Graham-Kendall) administered to the children. These groups are followed-up 12-15 months after the initial assessment. A sample of leukemia patients who have not received CNS treatment and their sibs and a sample of cystic fibrosis patients and their sibs are also being assessed using these procedures to control for effects other than CNS treatment. A second study deals with another sample studied prospectively. In this instance children in remission from leukemia are evaluated on the same battery of psychological tests as in the first study. They are tested just prior to prophylactic CNS treatment and are reevaluated one year later to determine if any possible brain changes brought on by the CNS treatment have resulted in learning disabilities and diminished intellectual functioning. The healthy siblings of the leukemics receiving CNS treatment, who are being studied retrospectively, will be used as a control group to check testing effects.

50. CHEMOTHERAPY OF CHILDHOOD LEUKEMIA AND SOLID TUMORS

Kung, F. H., University of California, San Diego Campus, School of Medicine, Dept. of Medicine, *P.O. Box 109, La Jolla, California*, 92093, United States of America

This is part of a broader project. A summary of this subproject is not available.

51. DIFFUSE PNEUMONIA IN LEUKEMIC CHILDREN

Sanyal, S., St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

52. TREATMENT OF RECURRENT CHILDHOOD LEUKEMIA

Rivera, G., St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

53. EFFECTIVENESS OF ANTI-VARICELLA TRANSFER FACTOR IN NON-IMMUNE LEUKEMIC CHILD

Humphrey, G. B., University of Oklahoma, Health Science Center, School of Medicine, Dept. of Pediatrics, *Box 26901, Oklahoma City, Oklahoma*, 73190, United States of America

This is part of a broader project. A summary of this subproject is not available.

C. THERAPY OF LEUKEMIA IN ADULTS AND UNSPECIFIED AGE GROUPS

1. CHEMOTHERAPY OF ACUTE MYELOGENOUS AND ACUTE NONLYMPHOCYTIC LEUKEMIA

54. LEUKEMIA 78 - TREATMENT OF ADULT ACUTE MYELOGENOUS LEUKEMIA

Palva, I., Hatanpaa Hospital, *33100 Tampere 10, Finland*

OBJECTIVE: The main objective is obtaining optimal results in the treatment of acute leukemia in adults on a nationwide scale. The specific objectives of this study are to determine the influence of different dosage schedules of the same drugs given in the same total doses, to verify the favorable effect of levamisole in the maintenance of remission, and to find out if prophylaxis of meningeal leukemia is useful in myelogenous leukemia in adults.

APPROACH: All new patients with acute myelogenous leukemia (15-65 years) in the 10 participating hospitals are randomized into two initial treatment schedules, both consisting of daunorubicine, cytarabine and prednisolone. The first course of the more aggressive option consists of triple the amount of cytostatic drugs used in the first course; the second, if needed, is the 'light ' one. After consolidation of the remission, half of the patients receive i.t. methotrexate as CNS prophylaxis. The maintenance consists of thioguanine with weekly injections of cytarabine; half the patients receive levamisole as well.

PROGRESS: The protocol was initiated on January 1, 1978, and 100 patients are expected to be enrolled by the end of 1980.

55. CHEMOIMMUNOTHERAPY OF ACUTE MYELOCYTIC LEUKEMIA

Holland, J. F., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

The Contractor shall exert its best efforts to evaluate the therapeutic effectiveness of inoculation with allogeneic acute myelogenous leukemia (AML) cells and with MER in acute myelocytic leukemia. These modalities shall be tested in a protocol which will utilize cytosine arabinoside and daunorubicin for remission induction followed by cycles of four different designated combinations of chemotherapy administered intermittently. The immunotherapy shall be interspersed with the first eight cycles of the chemotherapy courses. After appropriate stratification, eligible patients shall be randomized to: no immunotherapy; immunotherapy with neuraminidase-treated allogeneic cells; or immunotherapy with MER and neuraminidase-treated cells. The no-therapy arm of this regimen corresponds to a similar control group to be evaluated by the acute leukemia group B, and for this reason, the relative numbers of patients to be allocated to each arm of this protocol will be 1:2:2 respectively.

56. DETERMINANTS OF RESPONSE IN ACUTE MYELOCYTIC LEUKEMIA

Preisler, H. D., Roswell Park Memorial Inst., Dept. of Medical Oncology, *666 Elm St., Buffalo, New York*, 14263, United States of America

OBJECTIVE: Determine the factors which determine the response of patients to treatment for AML.

APPROACH: This study will integrate a patient's clinical characteristics with measurement of cell cycle characteristics and drug sensitivity of his leukemic cells so that an estimation of the likelihood of a favorable response to chemotherapy can be made. Studies of previously untreated patients and of patients with relapsed disease, as well as the serial study of patients throughout the course of the disease, will permit the recognition of more factors which change during the course of the disease and result in the development of resistance to therapy.

57. CHEMOTHERAPY AND CHEMOIMMUNOTHERAPY OF CANCER

Holland, J. F., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

In the last calendar year, Program Project Grant (CA15936-05) has been vigorously pursued by the investigators of the Mount Sinai School of Medicine under the Principal Investigatorship of James F. Holland, M.D.

Chemoimmunotherapy of acute myelocytic leukemia continues to provide exciting data.

Research in lung cancer has involved the investigation of a 4-drug combination regimen, MACC plus levamisole, and MACC plus C. parvum.

Our investigation of 4-drug second line chemotherapeutic responses in disseminated breast cancer continues to be productive.

Adriamycin and platinum continue to be the central building blocks for chemotherapeutic regimens in patients with ovarian cancer.

A continuing assessment of our chemotherapeutic regimens in prostatic cancer identifies 15 of 19 responders with six of eight with measurable lesions showing 6% or greater regression of the disease. Remaining responders were all characterized by major reduction in pain and reduction in alkaline and acid phosphatase.

Gastrointestinal cancer investigations continue with a central attention to fluorouracil by continuous infusion and intermittent intravenous bolus dosing with mitomycin-C and oral treatment with hexylmethylmelanamine.

Experimental chemotherapy has included active clinical investigations of several new drugs, m-AMSA, maytansine, dichloromethotrexate, L-phosphonoacetyl-l-aspartate (PALA), indocine-n-oxide, and L-alanosine.

In the microbiological research, serum opsonins as the determinant of success in granulocyte transfusions continue under study.

Analytical biochemistry of opportunistic infections has made major progress in identification of D-arabinitol, a metabolite of Candida albicans which can be reproducibly quantified in human serum.

BIBLIOGRAPHIC REFERENCES: Takahashi, I., Ohnuma, T., and Holland, J.F.: Comparison of biological effects of dichloromethotrexate and methotrexate on human leukemia cells in culture. Cancer Res. 39:1264-1268, 1979. Ambinder, E.P., Perloff, M., Ohnuma, T., Biller, H.F., and Holland, J.F.: High dose methotrexate followed by citrovorum factor reversal in patients with advanced cancer. Cancer 43:1177-1182, 1979.

58. LITHIUM INDUCED GRANULOCYTOSIS IN CANCER PATIENTS

Stein, R. S., Greco, F. A., Flexner, J. M., Vanderbilt University, School of Medicine, Dept. of Medicine, *21st Ave. S. & Garland, Nashville, Tennessee*, 37232, United States of America

This project studies the mechanisms of lithium induced granulocytosis and assesses the clinical significance of the phenomenon by means of clinical trials in acute myelogenous leukemia (AML), severe neutropenia, and hematologic malignancies. In a randomized trial in patients receiving cytosine arabinoside-daunomycin therapy for AML the duration of neutropenia (granulocytes less than 1000/mm3) is shorter in patients receiving lithium than in controls (16.0 vs. 24.6 days, p equals .013). Therapeutic levels have been maintained without significant drug toxicity. A cooperative group trial to determine if lithium affects duration of remission or tolerance of maintenance therapy has been instituted.

In patients with severe neutropenia, favorable responses to lithium (granulocyte increase greater than 300/mm3, and greater than 30% over baseline) have been seen in 11 of 23 patients with marrow failure uncomplicated by hypersplenism or acute leukemia. Our trial of lithium in patients receiving combination chemotherapy for Hodgkin's disease, lymphoma, or other malignancies has been instituted but it is too early for the evaluation of the data.

Studies of dose optimization have suggested that any lithium dose from 900 to 1500 mg/day can produce granulocytosis and that within this range, and serum levels of 0.5 to 1.5 meq./L, there is no correlation between lithium level and granulocyte response.

BIBLIOGRAPHIC REFERENCES: Stein, R.S., Flexner, J.M., Graber, S.: Lithium and granulocytopenia during induction therapy of acute myelogenous leukemia. Blood 54:636-641, 1979. Stein, R.S., Golomb, H.M., Diggs, C.H., Mauch, P., Hellman, S., Wiernik, P.H., Ultmann, J.E., and Rosenthal, D.S.: Anatomical substages of stage III-A Hodgkin's disease: a collaborative study. Ann. Intern. Med. 92:159-165, 1980.

59. NEUTROPHILIC GRANULOCYTOPOIESIS IN NORMAL MAN AND IN LEUKEMIAS

Cronkite, E. P., Miller, M., Chanana, A. D., Burlington, H., Carsten, A. L., Zucker, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Nuclear Medicine Service, *Middleville Rd., Northport, New York*, 11768, United States of America

The first aim is to obtain better insight into hemopoietic proliferation, particularly granulocytopoiesis, and its regulation in health and in blood diseases. The second aim is development of a method to determine the sensitivity of acute leukemia (AML) cells to chemotherapeutic agents to preselect the most effective drug(s) for therapy. The studies use diffusion chamber (DC) cultures and other in vitro culture systems. Tissue cultures are used, since in vivo study of cell proliferation with radioactive precursors of DNA can be used in man only to a very limited extent. Non-T, non-B, non-phagocytic, unidensity, mononuclear cells will be obtained from human blood and marrow. These cells will be cultured in DC's, in irradiated and non-irradiated hosts and with the addition of 'pure' populations of monocytes and neutrophils to study the cellular and humoral factors influencing the proliferation and differentiation of stem cells. The stem cell concentration in blood and marrow will be determined in DC's, agar DC's (ADC's) and in vitro soft agar dishes to determine morphology, potency to produce diverse cell lines and the number of cells produced per stem cell. Efforts will be made to show existence of and characterize 'pluricellpoietin,' an assumed regulator of stem cell proliferation. Human AML cells will be cultured in DC's, ADC's, and double diffusion chambers to determine whether these cells mature in a non-leukemic environment, and they will be mixed with normal marrow cells to see if they suppress normal stem cell differentiation and if they produce a factor that suppresses normal granulopoiesis. AML cells will be exposed to PHA and then subcultured in DC to develop a system of rapid growth in which it may be practical to assay the effectiveness of chemotherapeutic agents and preselect drugs for leukemia therapy. Peritoneal lavage studies in dogs will be continued to separate the leukocytosis-inducing factor and colony-stimulating factor by column chromatography. The purified forms of these factors will be tested in dogs to evaluate the in vivo role of the factors as regulators of granulocytopoiesis.

60. DETERMINATION OF DRUG SENSITIVITY OF HUMAN MYELOBLASTIC LEUKEMIA CELLS

Epstein, J., Roswell Park Memorial Inst., Dept. of Medicine A, *666 Elm St., Buffalo, New York*, 14263, United States of America

We will develop methods for the determination of the sensitivity of human myeloblastic leukemia cells to chemotherapeutic drugs. We will use the RF/UN mouse leukemia model to determine which of the in vitro clonogenicity methods best reflect the response of the leukemic stem cells to the different drugs. We will compare the responses of the cells which form colonies in agar, plasma and fibrin clots (CFUc and CFUd) to those of the leukemic stem cells in the spleen colony assay in the in vivo malignancy assay system. We will then determine the ability of one or more nonclonogenic in vitro assays to substitute for clonogenic or stem cell assays and adopt this assay to human bone marrow and peripheral blood leukemic cells. Such assays include the effects of drugs on precursor incorporation into macromolecules determined by scintillation counting and by autoradiographic techniques, and flow microfluorometry in single and dual parameter analyses to determine drug-induced perturbations in size, DNA, RNA and protein contents, cell cycle traverse, viability and, in conjugation with antinucleoside antibodies, to detect drug-induced breaks in DNA. We will develop drug resistant mouse leukemic cell lines which will be used to test the sensitivity of each assay to detect small numbers of resistant cells in the population. We will than study cells of relapsed AML patients to determine the ability of the assays which were found to reflect the sensitivity to a drug of the leukemic stem cells in the clonogenicity assay to predict response to drug therapy in man.

61. KINETICS OF SUBPOPULATION OF HUMAN LEUKEMIC CELLS

Tura, S., Santucci, M., Gobbi, M., Ricci, P., Ruggero, D., Baccarani, M., St. Orsola's University Hospital, Dept. of Hematology, *40138 Bologna, Italy*

It is planned to study several cytokinetic parameters of leukemic cells, in vivo and/or in vitro, after separation of leukemic cells into at least two subpopulations that could be distinguished by cytological, cytochemical or other criteria, reflecting their degree of maturation. The aim of this study is to investigate whether leukemic cells behave kinetically as a single population or whether they show different kinetic patterns. This has to be studied both under undisturbed conditions (prior to any therapy) and after administration of cytotoxics, in order to establish whether different subpopulations react differently to the same drug. The ultimate goal of this program is to provide further support for the use of kinetic information in planning leukemia therapy.

The first objective of this investigation is to determine the IM and the in vitro 3H-TdR IL of leukemic cells, prior to any therapy, in acute myeloid and lymphoid leukemia, after cell separation according to the degree of peroxidase-positivity and PAS-positivity, respectively. This study is in progress, but data are too scarce at present to allow presentation of preliminary results. The second objective is to investigate, in vivo and in vitro, the kinetics of an apparently highly homogeneous cell populaton, i.e., promyelocytes of acute promyelocytic leukemia (APL). Nine cases were studied by determining the IM and the IL in vivo of leukemic marrow cells, and their kinetic behavior in vitro (culture in methylcellulose with leukocyte-conditioned medium). The proliferative activity of leukemic promyelocytes was shown to be much lower, as compared with normal precursors, as well as with other less homogeneous and less mature myeloid leukemias.

Investigation of cell kinetic effects of cytotoxic drugs included arabinosyl cytosine (ARA-C) and its 2,2'-anhydro-derivative, cyclocytidine (CYCLO-C). The effect of single and repeated shots of ARA-C was determined in two patients with pH1-positive chronic myeloid leukemia (CML) in blastic phase. In both cases, non-granulated blast cells (myeloblasts, MB) were more perturbed by the drug than promyelocytes and myelocytes (PMC plus MC). MB were first blocked in the S phase (as shown by an early drop in the IM); thereafter they were pooled up in the S phase ('synchronization'). In contrast, PMC plus MC were not accumulated in the S phase. (Text Abridged.)

62. BONE MARROW CULTURE IN ACUTE MYELOID LEUKEMIA

Francis, G. E., University of London, Dept. of Hematology, c/o The Royal Free Hospital, *Pond Street, London NW3 2QG, England, United Kingdom*

OBJECTIVES: 1. To assess the role of stimulators of granulopoiesis in determining the response to induction chemotherapy in acute myeloid leukemia. 2. To analyze the changes in physical and functional properties of normal granulocyte-monocyte progenitor (clone-forming) cells which occur as these cells differentiate down the granulocyte-monocyte pathway and to compare these with the properties of equivalent AML clone-forming cells in order to distinguish genuine abnormalities of the leukemic cells from properties reflecting differences in maturity between AML and normal clone-forming cells.

APPROACH: 1. In vitro techniques will be used to assess the responsiveness of leukemic cells to colony stimulating factors (CSF) and to assay CSF levels in leukemic patients both before and during therapy. Response to agents known to increase CSF will be monitored. 2. Assays of responsiveness of cells will be used in combination with cell separation techniques which exploit physical and functional properties to achieve separation.

PROGRESS: This is a new project.

63. DIFFERENTIATION OF LEUKEMIA CELLS

Terada, M., Ministry of Health & Welfare, National Cancer Center, Section of Prevention of Carcinogenesis, *5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Tokyo, Japan*

The summary for this project is under entry no. 2.

64. ANTIBIOTIC PROPHYLAXIS IN THE MANAGEMENT OF ACUTE LEUKEMIA AND ITS EFFECTS ON THE PATIENTS' MICROFLORA

Catovsky, D., Darrell, J., Medical Research Council, Leukaemia Unit, Dept. of Bacteriology, *Du Cane Rd., c/o Royal Postgrad. Med. Sch., London W12 0HS, England, United Kingdom*

A combined clinicobacteriological study is proposed to examine whether the prophylactic use of co-trimoxazole alone or in combination with non-absorbable antibotics is effective in decreasing the rate of infection in neutropenic patients treated for acute leukemia. The laboratory studies will be directed to the investigation of changes in the gut and other body microflora resulting from the above regimens and seeking correlations between bacteriology data and clinical outcome.

It is proposed to enter in the study all patients suffering from acute myeloid leukemia admitted for cytotoxic treatment in the Dacie ward during a 2-year period. All patients will, on admission, be put on an antifungal regimen and on a rigorous regimen for skin, nose and throat antisepsis. They will be randomized to receive 24 hours later either: (a) co-trimoxazole alone twice daily, or (b) co-trimoxazole as above plus gut decontamination with framycetin and colistin, four times a day. Patients will be monitored with mutliple swabs and samples from various tissues. Bacteriological screening will be done twice weekly. Fecal specimens will be cultured aerobically and anaerobically and gas liquid chromatography (GLC) will be performed on these. End-point. (1) Clinical remission with recovery of neutrophils to 1 x 10 to the 9th power over 1 or (2) sustained fever (greater than or equal to 38 degrees C) for 2 hours and the commencement of systemic antibiotics will constitute the end points for clinical analysis.

65. STUDIES ON THE MECHANISM OF ACTION AND OF RESISTANCE OF PURINE AND PYRIMIDINE ANTIMETABOLITES

Brox, L. W., University of Alberta, Cancer Research Unit, McEachern Laboratory, *Edmonton, Alberta*, T6G 2H7, Canada

OBJECTIVE: The work in this laboratory is mainly directed at attempting to define parameters contributing to the development of the acquired drug resistance observed in clinical oncology. The systems being investigated are drug refractory adult acute myelogenous leukemia and multiple myeloma.

APPROACH: In general, two approaches are being pursued. Firstly, we are attempting to determine to what extent selection of biochemically resistant cell populations is contributing to the development of acquired drug resistance. For instance in the AML system we are looking for evidence for the selection of leukemic cell populations in which DNA synthesis is no longer inhibited by araC. It is also planned to look for cell populations in which extended araC-induced inhibition of DNA synthesis is more readily reversed upon removal of the drug. In the multiple myeloma system we are studying melphalan uptake, DNA alkylation and alkylation induced repair systems. As a consequence of the mixed cell types present in human bone marrow samples much of our work must be done by radioautography.

Our second avenue of investigation is to examine the possibility that drug induced alterations in host metabolism may result in significantly altered drug pharmacokinetics. The rationale here is that it is conceivable that even relatively small reductions in either drug exposure time or concentration may significantly reduce the degree of cell kill which may be attained. More extensive pharmacology studies will be carried out on araC and deoxycytidine in AML patients, and on melphalan and its hydrolysis products in the multiple myeloma system. These studies will make use of high performance liquid chromatography techniques and various radioimmunoassays which we have under development.

66. COLLABORATIVE THERAPEUTIC RESEARCH IN HUMAN LEUKEMIA

Frei, E., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

We will continue our multidisciplinary program of clinical research to improve the treatment of acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML). The chemotherapy innovations involve intensive and rotational therapy of chemotherapeutic agents in remission in patients with AML in attempt to maximize leukemia cytoreduction and minimize the development of drug resistance.

In acute lymphocytic leukemia (ALL) the major chemotherapeutic thrust will relate to the development of modified and new programs for prognostic subcategories of ALL.

Clinical pharmacologic studies of established agents as well as new agents will be conducted in parallel with the clinical therapeutic research.

BIBLIOGRAPHIC REFERENCES: Weinstein, H. J., Mayer, R. J., Rosenthal, D. S., Camitta, B. M., Nathan, D. G., and Frei, E., III: Childhood and Adult Myelogenous Leukemia (AML); Prolonged Unmaintained Remission After Intensive Sequential Combination Chemotherapy (SCC). American Society of Clinical Oncology, May, 1979, Abstract C-148.

67. EFFECTS OF THERAPY ON TUMOR-SPECIFIC IMMUNITY

Mitchell, M. S., University of Southern California, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

We propose to study the effects of chemotherapy and immunotherapy on immunity to autochthonous or allogeneic tumor cells ('tumor-specific' immunity) in patients with a solid tumor or acute leukemia. A large proportion of the tumor cells obtained by biopsy will be stored in DMSO at minus 70 degrees, to permit replacement of tissue cultures after 3 month continuous passage to minimize nonspecific lysis. Blood mononuclear cells and serum will be obtained weekly or biweekly from each patient before, during and after therapy in studies ranging from 6 weeks to 2 years. Clinical response to therapy will be measured objectively. Cell-mediated cytotoxicity will be measured by a 48-hour assay in 16 mm in diameter plastic wells, with 3H-proline or 125IUdR-labeled tumor cells. Blocking factor will be estimated by preincubating serum and tumor cells before adding mononuclear cells. Cytophilic antibodies will be titrated by the arming of mouse monocytes to form rosettes with tumor cells, while related antibody sensitizing for antibody-dependent cellular cytotoxicity (ADCC) will be titrated by the arming of neutral human monocytes to lyse tumor cells. 'Nonspecific' cytotoxicity will be studied by examining stratified populations of 'normal' individuals for reactivity, and by determining whether continuously cultivated tumor cells become overly sensitive to lysis. It will be established which subpopulations of mononuclear cells are the major cytotoxic effectors and their specificity will be determined. Lymph node cells of melanoma patients receiving intralymphatic immunotherapy with MER will be compared with blood lymphocytes. Patients with acute myelocytic leukemia given immunotherapy will be studied to discern whether humoral immunity to the leukemia is improved. We hope to determine whether our current regimens of tumoricidal therapy suppressive towards tumor-specific immunity, and whether putative immunotherapeutic regimens are stimulatory.

BIBLIOGRAPHIC REFERENCES: Rao, V.S., Grodzicki, R.L., and Mitchell, M.S. Specific in vivo inhibition of macrophage receptors for cytophilic antibody by immune complexes. Cancer Res. 39: 174-182, 1979. Bennett, J.A., and Mitchell, M.S. Induction of suppressor cells by intravenous administration of Bacillus Calmette-Guerin and its modulation by cyclophosphamide. Biochem. Pharmacol. (Arnold Welch Festschrift) 1979, In press.

68. CHEMOTHERAPY OF HEMATOPOIETIC MALIGNANCIES

Krantz, S. B., Koury, M., Graber, S. E., Dessypris, E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *1310 24th Ave. S., Nashville, Tennessee*, 37203, United States of America

This work is considered a research project because of the use of experimental chemotherapeutic drugs not licensed by the FDA. It involves the treatment of patients with hematopoietic malignancies by these drugs according to protocols that have already been reported by other investigators. The two experimental drugs that are involved are daunomycin used with cytosine arabinoside for acute granulocytic leukemia and folinic acid used with Cytoxan, Oncovin, methotrexate and cytosine arabinoside for the treatment of transformed cell lymphoma. In the past year three patients with acute leukemia were treated with the former protocol. All three went into remission and are in remission at the present time. No patients with transformed cell lymphoma were entered into the second protocol in the past year. Patients treated with these two protocols in prior years are still being followed to determine their ultimate survival.

69. CELLULAR PHARMACOLOGY OF CANCER CHEMOTHERAPEUTICS - USE OF CARRIER TO INCREASE THE SELECTIVITY OF THE DRUGS

Peterson, C. O., Paul, C., Kumlien, G., Vitols, S., Karolinska Institutet, Dept. of Pharmacology, *Solnavagen 1, S10401 Stockholm 60, Sweden*

OBJECTIVES: To study the cellular pharmacology of cancer chemotherapeutics, particularly anthracycline, in free form and linked to DNA as a carrier. To correlate the clinical effects of free and DNA-linked daunorubicin and adriamycin against acute non-lymphoblastic leukemia in adults to the cellular pharmacology of the drugs in the leukemia cells.

APPRAOCH: The Leukaemia Group of Central Sweden is conducting a clinical study to compare the effects of free and DNA-bound daunorubicin (in combination with ARA-C) against acute non-lymphoblastic leukemia in adults. The cellular uptake, subcellular localization and metabolism of the drugs are studied in vitro and in vivo in human leukemia cells, experimental leukemia and normal mice bone marrow cells as well as in rat myocytes. The anthracyclines are quantified by fluorometry after separation of metabolites by HPLC. The subcellular localization of the drugs is determined by isopyknic centrifugation of homogenates and analyses of drugs and marker enzymes.

PROGRESS: For induction of remission, free and DNA-bound daunorubicin seem to be equally effective, with response rates around 70 percent. Clinical and experimental results indicate that the DNA-complex is less cardiotoxic. After administration of free and DNA-linked adriamycin to leukemic patients in the same dose at different courses, the adriamycin levels not only in plasma but also in leukemia cells are much higher after the drug has been given as a DNA-complex.

70. AUTOLOGOUS MARROW AND PERIPHERAL BLOOD HEMATOPOIETIC STEM CELLS IN ACUTE LEUKEMIA - HARVESTING, CRYOPRESERVATION, REINFUSION

Rybka, W. B., Montreal General Hospital, Research Institute, *1650 Cedar Ave., Montreal, Quebec*, H3G 1A4, Canada

OBJECTIVE: To determine if autologous cryopreserved peripheral blood hematopoietic stem cells have any advantage over marrow cells in the therapy of acute leukemia.

APPROACH: In adult patients with either acute lymphoblastic leukemia or acute non-lymphoblastic leukemia, harvesting of hematopoietic stem cells from the marrow and peripheral blood will be undertaken. The quantity of circulating granulocyte precursors (CFUc) as a function of time following certain courses of chemotherapy will be determined. A comparison of growth characteristics in culture of leukemic blasts and normal remission cells will be undertaken. After determining the optimum time for harvesting remission hematopoietic stem cells, both marrow and peripheral blood cells will be harvested. These cells will be subsequently frozen and stored. The conditions of cryopreservation and storage will be closely observed. When the patients, so studied, relapse on conventional chemotherapy, they will be offered treatment with high dose cyclophosphamide and total body irradiation, a regimen known to eradicate leukemic cells in the hope of providing a prolonged remission. Marrow repopulation will be attempted with cryopreserved autologous cells. The repopulation ability of peripheral blood cells will be assessed.

71. STEROID RECEPTORS AND HORMONE SENSITIVITY OF HUMAN LEUKEMIAS

Nanni, P., Galli, M. C., Prodi, G., Gobbi, M., Universita degli Studi di Bologna, Istituto di Cancerologia, *via S. Giacomo 14, 40126 Bologna, Italy*

OBJECTIVE: To test a correlation among different parameters of steroid receptors, in vitro steroid sensitivity of lymphocytes and pharmacological therapy in patients with leukemias.

APPROACH: The levels of steroid receptors are measured using the standard method of dextrane-coated charcoal (DCC) on cytosol and the method of Lippman and Barr (J. Immunol., 118, 1977-1981, 1977) on viable cells.

Steroid sensitivity of leukemic cells is studied in terms of steroid-induced inhibition of precursors in incorporation into nucleic acids.

These data are correlated with clinical parameters of lymphoblastic and non-lymphoblastic leukemias and lymphomas.

72. TREATMENT OF ADULT ACUTE NON-LYMPHOCYTIC LEUKEMIA FOR PATIENTS LESS THAN 60 YEARS OF AGE

Appelbaum, F. R., Fefer, A., Buckner, C. D., Thomas, E. D., Cheever, M. A., Greenberg, P. D., University of Washington, School of Medicine, Dept. of Medicine, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The objectives of this study are: 1) to determine the complete remission rate with intensive induction therapy in patients less than 50 years of age; 2) to determine if more intensive induction and consolidation will decrease the rate of relapse in the first six months; 3) to compare the duration of remission and survival of patients receiving intensification at six and twelve months with or without monthly maintenance therapy; and 4) to determine the remission duration and overall survival of patients treated by Cytoxan and total body irradiation with an HLA-matched sibling bone marrow transplant while in first remission and to compare the results with the results obtained in those patients who achieve a remission and who are continued on chemotherapy. Patients entered in the study will be initially treated with intensive induction therapy including daunomycin, Ara-C, 6-TG, prednisone, and vincristine. Following the achievement of remission those patients who have HLA-matched siblings will be offered bone marrow transplantation while in first remission. Patients not having matched siblings and those refusing such transplants will be continued on chemotherapy. Patients not transplanted will receive two more cycles of intensive consolidation therapy: following maintenance therapy and late intensification at six and twelve months or late intensification alone. To date over fifty patients have entered this protocol. The initial complete remission rate has been over 75 percent. Further conclusions as to the progress of this protocol are premature.

73. ACUTE LEUKEMIA AFTER RADIATION AND/OR CHEMOTHERAPY

Rowley, J. D., University of Chicago, Pritzker School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

The occurrence of acute leukemia after treatment of a primary malignancy is a problem of increasing concern to clinical oncologists. It is not clear if these patients are particularly cancer-prone, or if the treatment regimen, radiation, chemotherapy, or a combination of the two, induces the leukemic transformation.

I have just completed the chromosome analysis with banding of leukemic cells from 27 patients with acute nonlymphocytic leukemia following treated malignant lymphoma and other malignancies. Except for one patient, every patient had a chromosomally abnormal clone of cells; 23 of the 26 patients were missing part or all of one No. 5 and/or one No. 7. In our 27 patients, the median time for the onset of leukemia was 59 months following the diagnosis of the original disease. Twenty-one patients had a preleukemic phase 2-20 months prior to overt leukemia.

I plan to study the role of the previous malignancy and the type of previous therapy by investigating bone marrow chromosomes in the following four groups of patients: (1) patients treated for malignant lymphoma, (2) breast cancer patients given preventative chemotherapy post-operatively, (3) patients with gynecological malignancies, particularly ovarian cancer, treated with an alkylating agent, and (4) post-renal transplant patients. A bone marrow aspiration will be obtained from each patient initially and approximately every two years thereafter. An abnormal karyotype in a patient who previously was normal would confirm the diagnosis of a preleukemic phase.

This investigation will establish whether nonrandom chromosome changes can be detected prior to the development of leukemia and whether the frequency and type of abnormality are different in the various clinical groups or can be related to the type of treatment regimen. This study will contribute to our understanding of the role of chromosome abnormalities in leukemogenesis, and permit the earlier detection of patients at risk.

74. AN EVALUATION OF THE EFFECT OF CHEMOTHERAPY AND ORAL ANTIBIOTICS ON GASTROINTESTINAL FUNCTION

Grove, W. R., Fortner, C. L., Schimpff, S. C., Newman, K. A., Lamy, P. P., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Research Pharmacy Section, *Baltimore, Maryland*, 21201, United States of America

The objective of this study is to evaluate the effect of chemotherapy and oral antibiotics on gastrointestinal function in a population of patients with acute nonlymphocytic leukemia in remission.

Eligible patients are those who are receiving the chemotherapy combination of thioguanine and cytosine arabinoside as maintenance chemotherapy and any of the following combinations of oral antibiotics for infection prevention: gentamicin plus nystatin; gentamicin plus vancomycin plus nystatin; nalidixic acid plus nystatin; trimethoprim sulfamethoxazole plus nystatin.

The following laboratory tests are performed as a baseline, repeated at the end of the chemotherapy course and again when patients are given oral antibiotics: serum carotene, serum vitamin A, serum folic acid, serum D-xylose (2 hr) and urine D-xylose (5 hr).

Sixteen patients have been entered on study. Seven patients have completed the sequence of laboratory tests. Eight patients failed to complete the tests, mostly due to the need for hospitalization to receive systemic empiric antibiotics. One patient remains on study. Additional patients will be entered on the study as they begin their maintenance courses of chemotherapy. It is too early to evaluate the data.

75. GROWTH KINETICS AND DRUG RESPONSE OF CELL POPULATIONS

Fried, J., Clarkson, B. D., Arlin, Z. A., Hansen, H. J., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

Bone marrow samples from patients with acute nonlymphocytic leukemia will be obtained at intervals prior to and during early therapy with the three-drug combination consisting of cytosine arabinoside, daunorubicin, and 6-thioguanine. Samples will be stained with a flurorescent dye and analyzed for DNA content by flow cytometry. The principal objectives of these studies will be to determine whether synchronization and/or recruitment occurs, and whether any kinetic effects observed can be related to the observed clinical response.

Additional patients with other leukemias and lymphomas will be monitored by flow cytometry, especially those with high growth fractions. In these studies we will attempt to determine whether any observed drug-induced perturbations in cell cycle progression can by exploited therapeutically. For patients in relapse or resistant to standard therapy, experimental drugs or drug combinations will be tested, including acridinyl anisidide (AMSA), high dose thymidine, and others.

Cell cultures will also be used to explore the possible kinetic basis for any observed cytotoxic and/or synergistic effects of the drugs employed in patient treatment. In addition, they will be used to test new or revised fluorescent staining methods used in flow cytometry.

We will also test the feasibility of using the fluorochromes Hoechst 33258 and/or DAPI for the viable staining of tumor samples from patients with leukemia and lymphoma. The objective will be to study short-term kinetics following biopsy, utilizing the cell sorter to separate viable cells in various portions of the cell cycle.

BIBLIOGRAPHIC REFERENCES: Arlin, Z.A., Fried, J., and Clarkson, B.: Human acute leukemia. In: Flow Cytometry and Sorting (M. R. Melamed, P. F. Mullaney, M. L. Mendelsohn, eds.), John Wiley and Sons, Inc., New York, 1979, pp. 583-597. Fried, J., and Mandel, M.: Multi-user system for analysis of data from flow cytometry. Computer Programs in Biomedicine 10: 218-230, 1979.

76. THE CHEMOTHERAPY OF ADULT ACUTE LEUKEMIA

Wiernik, P. H., Schimpff, S., Schiffer, C., Aisner, J., Young, V. M., Sarin, P., Brenner, D., Van Sloten, K., Markus, S., Duffy, P., Breitman, T., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

A 7-day continuous intravenous infusion of cytosine arabinoside plus a 3-day schedule of intermittent daily doses of adriamycin has been shown to be as effective in the induction of remission in adults with acute nonlymphocytic leukemia as the combination of cytosine arabinoside with daunorubicin. A complete remission rate of 65% has been obtained with either combination. However, the adriamycin combination has been shown to be more toxic and to require more careful dosage adjustment and monitoring of blood levels. At present it is too early to discern whether the addition of either neuraminidase-treated allogeneic myeloblasts or splenectomy to chemotherapy during remission maintenance treatment enhances the duration of remission or survival of patients. Reverse transcriptase has been identified in the bone marrow cells of leukemia patients prior to treatment and in morphologically normal peripheral cells during complete remission. This may suggest that morphologically and functionally normal granulocytes in the peripheral blood of leukemia patients in complete remission may actually be derived from leukemic cells.

BIBLIOGRAPHIC REFERENCES: Wiernik, P.H.: Polycythemia. In Hartman, P.M. (Ed.): Guide to Hematologic Disorders, New York, Grune and Stratton, Inc., 1980, pp. 181-190. Chang, P., Wiernik, P.H.: Chapter 12: Leukemia. In Spivak, J.L. (Ed.): Fundamentals of Clinical Hematology, Hagerstown, Harper & Row, 1980.

2. CHEMOTHERAPY OF ACUTE LYMPHOCYTIC AND ACUTE LYMPHOBLASTIC LEUKEMIA

77. PLASMA METHOTREXATE ASSAYS IN ROUTINE TREATMENT FOR ACUTE LYMPHOCYTIC LEUKAEMIA

Marks, V., Aherne, G. W., Piall, E., University of Surrey, Dept. of Biochemistry, *Guildford GU2 5XH, England, United Kingdom*

OBJECTIVE; The reason why some children with ALL relapse, and others on the same regime do not, is obscure but one possibility is that absorption, plasma concentration and persistence of methotrexate are important variables. Certainly there is a great variation in both the frequency and quality of toxic effects encountered. It is proposed to measure plasma methotrexate levels following a standard oral dose in children with ALL in the MRC UK ALL v trial. Analysis of the results may indicate any correlation with toxic effects of methotrexate and with duration of remission.

APPROACH: Five blood samples taken over 5 hours following an oral dose of methotrexate will be collected after 6 months, 18 months and 2 1/2 years of treatment of ALL. The methotrexate concentration in the plasma will be measured by radioimmunoassay at the University of Surrey.

PROGRESS: In the course of studying a small number of patients (23) with ALL two groups of patients were distinguished. In one group the absorption of methotrexate following an oral dose was rapid and in the other - delayed. Patients in the 'slow absorption' group had significantly more drug after a longer period of time than those in the 'fast absorption' group. To date, another 150 series of plasma samples have been assayed but an analysis of the results has not yet been carried out.

78. ACUTE LYMPHOBLASTIC LEUKEMIA - COMBINATION CHEMOTHERAPY STUDIES

Lister, T. A., Bell, R., Brearley, R. L., Ford, J. M., Malpas, J. S., Greaves, M. F., Roberts, M. M., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

OPAL Study (oncovin, prednisolone, adriamycin, L-asparaginase). Entry to the OPAL study closed in February 1978. Complete remission was achieved in 44 out of 63 patients aged between 15 and 68 years of age. Twenty-two patients are still alive between 27 and 81 months and the median survival was 22 months. Survival of patients in whom complete remission was achieved was significantly better (P less than 0.001) than that of those in whom it was not achieved, with the median duration of remitters being 40 months compared with one month for non-remitters. Thirteen patients continue in first complete remission, with a median duration of complete remission of 26 months.

Examination of prognostic factors previously analyzed confirmed the favorable association between the presence of 'ALL antigen' on the cell surface and prolonged remission duration, and the unfavorable association between bulky disease, measured by hepatosplenomegaly and remission duration.

Follow-up continues.

HEAV D Study (combination therapy using adriamycin, cyclophosphamide, L-asparaginase, vincristine, and dexamethasone). In March 1978, the remission induction program for adult acute lymphoblastic leukemia was intensified with the objective of eliminating early relapse. The total dose of adriamycin was increased to a total of 450 mg/m2 and cyclophosphamide was added to all but the first two cycles. Central nervous system prophylaxis and maintenance therapy were identical with the OPAL program. Complete remission has been achieved in 8 out of 16 cases to date, with three further cases receiving therapy and one excluded for social reasons. Only one patient has relapsed (at 6 months) and the study continues.

79. EVALUATION OF INTENSIFICATION AND MAINTENANCE PROGRAMS IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA

Pavlovsky, S., Sackmann Muriel, F., Grupo Argentino de Tratamiento de la Leucemia Aguda, *P. de Melo 3081, 1425 Buenos Aires, Argentina*

DESCRIPTION: It is a comparative Phase III trial designed to answer the following questions concerning cases of acute lymphoblastic leukemia induced to achieve complete remission with the combination of vincristine and prednisone in patients who received adequate preventive CNS therapy with 2,400 rad of Co60 irradiation to the cranial-cervical region and simultaneously intrathecal methotrexate and dexamethasone: 1) Is a short intensification with cytosine arabinoside and cyclophosphamide immediately after complete remission useful? 2) Does the use of weekly doses of 6-mercaptopurine and methotrexate have the same maintenance effect as daily 6-mercaptopurine and twice weekly methotrexate? 3) Do further 3-month doses of intrathecal methotrexate and dexamethasone help to decrease still more the incidence of meningeal leukemia?

A total of 465 cases were entered of whom 390 were children and 75 were adults. This study was completed in December 1975.

A progress report was presented to the XIV International Congress of Pediatrics, and at the meeting of the American Association for Cancer Research, San Diego, May 1975. A complete report appeared in Cancer of October 1978.

80. KINETICS OF SUBPOPULATION OF HUMAN LEUKEMIC CELLS

Tura, S., Santucci, M., Gobbi, M., Ricci, P., Ruggero, D., Baccarani, M., St. Orsola's University Hospital, Dept. of Hematology, *40138 Bologna, Italy*

The summary for this project is under entry no. 61.

81. METHOTREXATE, ONCOVIN, L-ASPARAGINASE AND DEXAMETHASONE THERAPY FOR ADULTS WITH ACUTE LYMPHOCYTIC LEUKEMIA

Esterhay, R. J., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland,* 21201, United States of America

The purpose of this project is to improve the remission induction rate of acute lymphocytic leukemia in adult patients utilizing vincristine and dexamethasone with intermittent moderate doses of methotrexate followed by asparaginase. A second objective is to decrease the incidence of severe infections during induction therapy by utilizing oral non-absorbable antibiotics. A third objective is to determine whether intermittent high dose methotrexate with leucovorin rescue and with vincristine and dexamethasone will prolong remission duration. The fourth objective is to determine the efficacy of moderate and high dose methotrexate in preventing meningeal leukemia and to correlate the clinical effectiveness with the cerebrospinal fluid methotrexate levels. To date 33 patients have been entered onto this study. Eighteen patients had no prior treatment, fifteen had prior treatment. Of the no-prior-treatment patients, five patients are still on study and 13 are off study. Complete remissions have been achieved in 14 of the 18 (78%) patients that went through induction. Of the prior treatment patients, ten of thirteen (77%) achieved complete remission. The median survival for complete remission patients for both groups is 16-plus months and for all treated patients for both groups is 10-plus months.

82. CLINICAL AND BIOCHEMICAL CONSEQUENCES OF 2'-DEOXYCOFORMYCIN THERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA

Mitchell, B. S., University of Michigan, Ann Arbor Campus, Simpson Memorial Research Inst., Dept. of Internal Medicine, *Ann Arbor, Michigan,* 48104, United States of America

Congenital deficiency of the enzyme adenosine deaminase (ADA), which catalyzes the irreversible deamination of adenosine and deoxyadenosine, results in an immunodeficiency syndrome characterized by severe lymphopenia. Inhibitors of this enzyme are thus of considerable interest as potentially selective chemotherapeutic agents for lymphoproliferative malignancies. We propose to study the biochemical and clinical effects of 2'-deoxycoformycin, a potent ADA inhibitor, in patients with acute lymphoblastic leukemia and lymphoma. We wish to investigate 1) the clinical utility, 2) the pharmacology, 3) the mechanism of action, and 4) the biochemical and physiologic consequences of 2'-deoxycoformycin administration. In addition, we hope to develop an in vitro test which will predict the efficacy of 2'-deoxycoformycin therapy in actue leukemias and to identify a biochemical marker which may render certain lymphoid cells resistant to its cytotoxic effect(s). Biochemical parameters which will be followed in each patient will include red cell and lymphoblast ADA activity, S-adenosylhomocysteine (SAH) levels, SAH hydrolase activity, and deoxynucleoside triphosphate levels. Plasma and urinary levels of adenosine, deoxyadenosine and 2'-deoxycoformycin will be measured daily. 5'-nucleotidase activity and cytoplasmic deoxynucleotide degradatory activity will be measured in a wide variety of leukemic cells and correlated with the ability of these cells to accumulate deoxynucleotides in vitro. These studies should enhance our understanding of the mechanism(s) by which lymphoid cells are killed in ADA deficiency and provide basic foundation for the future use of 2'-deoxycoformycin in malignant lymphoproliferative diseases.

83. COLLABORATIVE THERAPEUTIC RESEARCH IN HUMAN LEUKEMIA

Frei, E., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

The summary for this project is under entry no. 66.

84. DISTRIBUTION AND FUNCTION OF LYMPHOID SUBPOPULATIONS IN ACUTE LYMPHOBLASTIC LEUKEMIAS AND LYMPHOMAS

Sen, L., Estevez, M. E., Finiasz, M., Diez, R., Guintoli, J., Instituto de Investigaciones Hematologicas, Depto. de Microbiologia, *Pacheco de Melo 3081, 1425 Buenos Aires, Argentina*

OBJECTIVES: To study the relationship between alterations in immunocompetent cells and in the development or progress of leukemias and lymphomas. To determine in untreated patients with ALL or lymphomas if the presence of blasts that express different markers is related to initial clinical parameters and response to treatment. To identify the area of cellular immune system affected by chemotherapy and determine if the immunosuppressive and immunomodulatory effects of treatment depend upon treatment duration. To determine the existence of tumor-specific antigens in lymphoblasts in ALL and lymphomas. To determine whether the reactivation of the immune system that follows the discontinuation of all chemotherapy in ALL patients is related to the individual clinical course.

METHOD: Studies will be performed at various stages of disease. All patients come from the Argentine Group for Treatment of Acute Leukemia (GATLA). Stage I: The characteristics of blast membrane in ALL and lymphomas prior to treatment will be studied. Stage II: During continuous and complete remission functional studies of the specific and non-specific immune system will be performed. Stage III. After three years of treatment and maintenance the patient in continuous and complete remission, upon suspension of treatment, will undergo studies on the distribution of lymphoid sub-populations and functional studies of the T and B systems and mononuclear phagocyte function.

PROGRESS: Our preliminary studies show that, in 58 patients studied, 9 were ALL-T; 42 were ALL null; 6 were ALL with C3; and 1 was ALL with receptors for rat red blood cells. Patients were followed for 3 to 28 months. In the ALL-T group 78% relapsed. In the ALL null group 10% relapsed. In the ALL C3 group 50% relapsed. At 19 months the patient with receptors for rat red blood cells is in complete and continuing remission. (Translated)

85. TREATMENT OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

Appelbaum, F. R., Fefer, A., Buckner, C. D., Thomas, E. D., Cheever, M. A., Greenberg, P. D., University of Washington, School of Medicine, Dept. of Medicine, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The objectives of the study are: 1) to determine the complete remission rate with intensive induction in adults with acute lymphoblastic leukemia; 2) to determine the overall survival of patients treated with intensive consolidation and maintenance therapy; and 3) to determine the remission duration and overall survival of patients treated with Cytoxan and total body irradiation and an HLA-matched sibling bone marrow transplant while in first remission and to compare the results with those obtained in patients who achieve a remission and are continued on chemotherapy. The approach of this study will be to treat adults with acute lymphoblastic leukemia with intensive induction therapy including vincristine, prednisone, L-asparaginase, and daunomycin. Patients achieving a complete remission who have HLA-matched siblings will be offered bone marrow transplantation while in the first remission. Those patients who lack HLA-matched siblings or who decide against a bone marrow transplant will be treated with intensive maintenance therapy. Maintenance therapy will include CNS prophylaxis and cyclical therapy with vincristine, prednisone, daunomycin, 6-mercaptopurine, and methotrexate. The number of patients entered in this study to date is too small to allow drawing any firm conclusions.

86. CHEMOTHERAPY AND CNS PROPHYLAXIS FOR ACUTE LYMPHOBLASTIC LEUKEMIA

McIntosh, L. S., Yale University, School of Medicine, Dept. of Pediatrics, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

87. AUTOLOGOUS MARROW AND PERIPHERAL BLOOD HEMATOPOIETIC STEM CELLS IN ACUTE LEUKEMIA - HARVESTING, CRYOPRESERVATION, REINFUSION

Rybka, W. B., Montreal General Hospital, Research Institute, *1650 Cedar Ave., Montreal, Quebec*, H3G 1A4, Canada

The summary for this project is under entry no. 70.

88. STEROID RECEPTORS AND HORMONE SENSITIVITY OF HUMAN LEUKEMIAS

Nanni, P., Galli, M. C., Prodi, G., Gobbi, M., Universita degli Studi di Bologna, Istituto di Cancerologia, *via S. Giacomo 14, 40126 Bologna, Italy*

The summary for this project is under entry no. 71.

89. TREATMENT OF HUMAN T-CELL LEUKEMIA

Yu, A. L., Bakay, B., Kung, F. H., Nyhan, W. L., University of California, San Diego Campus, School of Medicine, Dept. of Pediatrics, *P.O. Box 109, La Jolla, California*, 92093, United States of America

We propose to investigate the use of deoxycoformycin, a potent inhibitor of adenosine deaminase (ADA) in the treatment of human T-cell leukemia. In vitro effects of deoxycoformycin and other potentiating drugs on leukemic cells will be determined by measurement of DNA and protein synthesis in leukemic cells. The key enzymes involved in the metabolism of adenosine and deoxyadenosine will be analyzed in order to compare among different subtypes of acute lymphoblastic leukemia and to correlate the enzyme profiles with sensitivity to deoxycoformycin and other drugs. Based on these in vitro studies, clinical trials of deoxycoformycin and other potentiating agents will be conducted in patients whose leukemic cells display in vitro sensitivity. Optimal route, dosage and frequency of administering deoxycoformycin will be determined from pharmacokinetic studies of deoxycoformycin. The therapeutic responses to deoxycoformycin will be evaluated by observing clinical course, assessing leukemic cell burden and determining the viability of leukemic cells. The possible toxic side-effects of deoxycoformycin will be assessed by clinical observations and routine laboratory tests of functions of major organ systems, with special emphasis on hemotological and immunological systems. In addition, the purine metabolism in leukemia cells undergoing treatment with deoxycoformycin will be investigated by high pressure liquid chromatography to elucidate the molecular action of deoxycoformycin, and to obtain quantitative chemical measures by which to assess optimal dose schedules.

3. CHEMOTHERAPY OF CHRONIC MYELOGENOUS, AND CHRONIC LYMPHOCYTIC LEUKEMIA

90. TREATMENT OF THE RESISTANT PHASE OF CHRONIC MYELOGENOUS LEUKEMIA WITH 5-AZACYTIDINE AND VP16-213

Schiffer, C. A., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Cell Component Therapy Section, *Baltimore, Maryland*, 21201, United States of America

A total of 19 patients with CML in blast crisis have been treated with the combination of 5-azacytidine (150 mg/m2 IV in 3 divided doses) and VP16-213 (75 mg/m2 IV per day for a total of 5 days). Prompt antileukemic effect was seen in 16 of 17 evaluable patients, with one short complete response. Overall median survival was two months and response tended to be of short duration. Although the combination of 5-azacytidine and VP16 has activity in CML in blast crisis, responses have been of short duration, similarly to results achieved with other agents with this disorder.

91. VINDESINE TREATMENT FOR THE ACUTE PHASE OF CHRONIC GRANULOCYTIC LEUKEMIA

Strauss, J. F., Sheehan, R. G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology/Oncology Section, *4500 S. Lancaster Rd., Dallas, Texas*, 75216, United States of America

An acute phase of blast transformation phase eventually develops in the majority of patients with chronic granulocytic leukemia regardless of the initial therapy. The prognosis from the onset of the acute phase is poor. The course resembles that of acute leukemia and survival beyond six months is uncommon. Some of the drugs useful in acute leukemia may produce brief responses in some of the patients, but in most the course during the acute phase is not changed by currently available chemotherapy. Palliative and supportive measures important at this stage are treatment of infections and transfusions of red cells and platelets.

Since no drug has been established as effective treatment of the acute phase, studies continue to search for active drugs and possible prognostic indicators to identify those patients most likely to respond.

This study proposes to treat patients in the acute phase of chronic granulocytic leukemia with Vindesine, a new anti-neoplastic agent.

The drug is to be administered once a week by IV injection. Weekly evaluation of manifestations of leukemia is to be carried out. Patients determined to be responders without an undue toxicity are continued on weekly treatment for as long as hematologic improvement is maintained without unacceptable toxicity.

4. CHEMOTHERAPY OF ACUTE LEUKEMIAS AND LEUKEMIAS (UNSPECIFIED)

92. CELL KINETICS AND CHEMOTHERAPY IN ACUTE LEUKEMIA

Smets, L. A., Nederlands Kankerinstituut, Div. of Experimental Chemotherapy & Radiotherapy, *108 Sarphatistraat, Antoni van Leeuwenhoekhuis, Amsterdam, Netherlands*

OBJECTIVE: To apply pulse-cytophotometry to samples from bone marrow and peripheral blood of leukemia patients, characterize the disease and detect earlier the response of the individual patient to chemotherapy.

APPROACH: DNA per cell distributions were recorded by automated cytofluorometry (pulse-cytophotometry) in bone marrow aspirates and peripheral blood samples of leukemia and during chemotherapy. In most cases, early perturbations in DNA per cell histographs were observed, characteristically reflecting the known mode of action of the drugs. These changes, in general, preceded the clinical observation of drug response. The discovery of proliferating cells in the peripheral blood of patients with various hematological disorders was evaluated.

PROGRESS: In a series of 40 patients, 32 patients showed a positive correlation between early cytophotometric changes and clinical effects of chemotherapy, 7 patients were negative for both pulse-cytophotometric and clinical reactions, and 1 probably was false-positive in the pulse-cytophotometric assay. The validity of the assay for early detection of drug resistance in acute leukemia and related diseases is suggested by these results. A high percentage of proliferating cells in the peripheral blood relative to bone marrow activity seems to be associated with potentially leukemic disorders (preleukemic syndromes).

93. PHARMACODYNAMICS OF CYTOSINE ARABINOSIDE IN ACUTE LEUKEMIA

Drenthe Schonk, A., Wessels, J., Haanen, C., University Hospital of Nijmegen, Dept. of Internal Medicine, *Geert Grooteplein 10, 6525 GA Nijmegen, Netherlands*

OBJECTIVE: Investigation of interindividual variations in pharmacodynamics of cytosine arabinoside and the results of therapy.

APPROACH: Very sensitive tests have been developed to measure low concentrations of cytosine arabinoside and the phosphorylated products of the drug like Ara-CTP. The quantities of Ara-C and Ara-CTP are related to thymidine incorporation studies, cell proliferation properties and results of therapy.

PROGRESS: In 45 patients with acute leukemia, the phosphorylating capacity of individual leukemic blast cells varied considerably. In 23 patients the concentration of Ara-C leading to a 50% inhibition of DNA synthesis also varied tremendously. A new treatment scheme was developed with dosages 5-10 times higher than usual and with longer intervals (to 24 hours) which seems much more effective and less toxic than other therapy schemes which have been used until now.

94. CHEMOTHERAPY OF ACUTE LEUKEMIA AND RELATED DISORDERS

Kyle, R. A., Burgert, E. O., Gilchrist, G. S., Smithson, W. A., Hoagland, H. C., Greipp, P. R., Cupps, R. E., Soule, E. H., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

A prospective, randomized study involving chemotherapy of acute leukemia, multiple myeloma, malignant lymphoma and solid tumors is being included in the cooperative activities of Cancer and Leukemia Group B.

BIBLIOGRAPHIC REFERENCES: Kyle, R.A., Gailani, S., Seligman, B.R., Blom, J., McIntyre, O.R., Pajak, T.F., and Holland, J.F.: Multiple myeloma resistant to melphalan: Treatment with cyclophosphamide, prednisone, and BCNU. Cancer Treat. Rep., 63:1265-1269, 1979. Harris, R.B., Perry, H.O., Kyle, R.A., and Winkelmann, R.K.: Treatment of scleromyxedema with melphalan. Arch. Dermatol., 115:295-299, 1979.

95. CHEMOTHERAPY OF ACUTE LEUKEMIA (HUMAN)

McCredie, K. B., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Developmental Therapeutics, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

96. BETA-DEOXYTHIOGUANOSINE IN REFRACTORY ACUTE LEUKEMIA

Miller, D. S., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina*, 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

97. MECHANISM OF ACTION AND DISTRIBUTION OF NEW CHEMOTHERAPEUTIC AGENTS USED IN THE TREATMENT OF LEUKEMIA

Burchenal, J. H., Memorial Sloan Kettering Cancer Center, Laboratory of Applied Therapy, *1275 York Ave., New York, New York*, 10021, United States of America

The aims of this study are as follows: (1) To detect or develop agents which will be useful in the treatment of human leukemia. This is done by the evaluation of selected classes of compounds against a spectrum of strains of transplanted mouse leukemia sensitive to and resistant to conventional chemotherapeutic agents. (2) To study the mechanism of action of new antileukemic agents both in vivo in mouse leukemia and in vitro in cell cultures of mouse leukemias L5178Y, P815, L1210, or Burkitt's tumor, and human acute leukemia (a) by observing the reversal or potentiation of this antileukemic action by known compounds; (b) by observing cross-resistance or lack of cross-resistance with known antileukemic agents; (c) by observing cytocidal effects of new agents on proliferating and non-proliferating cells. (3) To study differences in toxicity, therapeutic activity, and total leukemic cell kill produced by various dosage schedules and combinations of agents. (4) To study new 2' or 3' halogenated, 2,2'- or 2,5'-anhydro and 5,6 dihydro disubstituted arabinofuranosyl, ribofuranosyl and xylofuranosyl pyrimidine derivatives and derivatives of 5-aza-cytidine, in hopes of obtaining increased antileukemic activity.

98. A PHASE II TRIAL OF NEOCARZINOSTATIN

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

Neocarzinostatin is an investigational drug to be used in patients with histologically confirmed carcinoma of the bladder, kidney, pancreas, stomach, uterus, and ovary, hepatoma, acute leukemia, or malignant melanoma after the usual first line treatments have been exhausted. The objectives of this study were to determine response frequency, response duration, and survival duration in patients treated and to determine the frequency and severity of organ system toxicities associated with Neocarzinostatin. This is part of a larger study and the results are not available at this time.

99. NEW DRUG THERAPY OF PREVIOUSLY TREATED ADULT LEUKEMIA

Van Echo, D. A., Wiernik, P. H., Markus, S., Aisner, J., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medical Oncology Section, *Baltimore, Maryland*, 21201, United States of America

Clinical studies have been undertaken to identify new agents or combinations of agents that may have activity in patients with relapsed acute leukemia. In 12 patients the combination of 5-azacytidine plus pyrazofurin and in 20 patients the single agent VP16-213 in high doses have both been found to be ineffective. AMSA used in 17 patients as a single dose and in 16 patients on a multiple dose schedule and the combination of cytosine arabinoside (ARA-C) plus thymidine (TdR) used in 28 patients both have shown significant antileukemic activity in patients with relapsed ALL and ANLL. The response rates (CR plus PR) in either of the last two studies is in the range of 30%-50%. These studies are continuing and it is still too early to develop stable response data.

BIBLIOGRAPHIC REFERENCES: Van Echo, D.A., Wiernik, P.H., Aisner, J.: High dose VP16-213 (NSC 141540) for the treatment of patients with previously treated acute leukemia. Cancer Clinical Trials, (in press), 1980. Van Echo, D.A., Chiuten, D.F., Markus, S., Wiernik, P.H.: A clinical trial of pyrazofurin in combination with 5-azacytidine in acute nonlymphocytic leukemia. Cancer Clinical Trials, 1980.

100. STRUCTURAL AND FUNCTIONAL STUDIES ON LEUKEMIC CELLS IN RELATION TO TREATMENT

Gunz, F. W., Vincent, P. C., Prosser, E. J., Muir, P. D., Zbroja, R., Kanematsu Memorial Inst., Dept. of Medical Research, *Macquarie St., Sydney, N.S.W. 2000, Australia*

OBJECTIVE: To explore abnormalities in the structure and function of leukemic leucocytes and to exploit these in the therapy of acute leukemia.

APPROACH: (a) Cytogenetics: Leukemic cells are studied cytogenetically by conventional and banding techniques. Serial studies are made of patients under treatment. (b) Studies on DNA and chromatin: DNA fractions, especially satellite hybridization methods. (c) Cell kinetics: The initial kinetic parameters of leukemic cells and the effects of attempted synchronization by means of hydroxyurea are determined by pulse cytophotometry of blood and marrow cells, specimens being obtained at selected intervals after drug administration.

PROGRESS: All methods have been well established. Consistent changes are being observed in banding patterns of acute leukemia cells. No differences have so far been found in highly purified satellite DNA fractions from normal and leukemic cells. Synchronization by means of hydroxyurea has been observed in at least half the patients studied, but there are considerable differences between patients in the degree and timing of the synchronization process.

101. REGULATION OF CELL PROLIFERATION IN NORMAL AND LEUKEMIC BONE MARROW WITH SPECIAL REFERENCE TO CHEMOTHERAPY

Laerum, O. D., Aardal, N. P., Bassoe, C. F., Morild, I., Universitetet i Bergen, Gade Inst., Dept. of Pathology, *5016 Haukeland Hospital, Bergen, Norway*

OBJECTIVE: a) Investigation of humoral regulators of hematopoietic cell proliferation. b) Cell kinetic response to chemotherapy in leukemia patients.

APPROACH: a) Cell cycle effects as well as target cell populations of partially purified extracts containing granulocyte chalone are investigated in different assay systems, including agar culture technique and diffusion chamber culture in vivo. b) The effect of different combination therapy schemes on cell cycle distribution of leukemia cells in peripheral blood are investigated with flow cytometry. This is done as a sequential study during the first five days of treatment of patients. The investigation is combined with cytochemical methods.

PROGRESS: a) Effects of granulocyte chalone extracts on the stem cell committed for myelopoiesis, as well as interaction with colony stimulating factor are studied. Cell cycle effects of the same extracts have been investigated in further detail. Some of this information has been published previously. Semipurified material of low molecular weight peptide from mature granulocyte has been studied in collaboration with Dr. W. Paukovits, Vienna. The factor interacts with myelopoietic colony formation in agar, and reversible inhibition can be obtained during a short exposure prior to plating in agar. b) With flow cytometry, an accumulation of cells with S-phase DNA content in peripheral blood is seen in patients with acute leukemia responding to combination chemotherapy (COAP and PRAP), and this is now under investigation in a larger number of patients.

102. MEASUREMENT OF CYTOTOXIC DRUGS BY RADIOIMMUNOASSAYS IN THE TREATMENT OF LEUKEMIA

Marks, V., Aherne, G. W., Piall, E., University of Surrey, Dept. of Biochemistry, *Guildford GU2 5XH, England, United Kingdom*

OBJECTIVE AND APPROACH: It is becoming increasingly important to measure drug blood level during cancer chemotherapy and there is an evident demand for sensitive, specific techniques that can handle large numbers of samples for analysis of drug concentrations. The complexity of chemotherapy demands that the mechanism of drug metabolism, elimination and handling is clearly understood. The technique of radioimmunoassay can provide the rapid and sensitive measurements of drugs in biological fluids that are required for this type of work. The purpose of this study is to develop radioimmunoassay techniques for several cytotoxic drugs used in the treatment of leukemia, e.g., methotrexate, adriamycin and cytosine arabinoside, and to apply these assays to determining various pharmacokinetic parameters in both the clinical and experimental situations.

PROGRESS: Radioimmunoassays for several cytotoxic drugs have now been developed including methotrexate, cytosine arabinoside, the Vinca alkaloids and bleomycin. Several clinical projects using these assays have been completed and valuable information gained; some are under way in collaboration with clinical centers throughout the country. Developmental work continues on a number of other cytotoxic drugs, e.g., adriamycin and daunomycin.

103. CYTOKINETICALLY DIRECTED CHEMOTHERAPY FOR LEUKEMIA AND MELANOMA

Barthel, B., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

104. LEUKEMIA CELL KINETICS AND CHEMOTHERAPY

Murphy, S., St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

105. DDMP FOR MENINGEAL LEUKEMIA (HUMAN, DOGS)

Rundles, R. W., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina*, 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

106. THE ESTIMATION AND CLINICAL SIGNIFICANCE OF PLASMA AND CELLULAR CONCENTRATIONS OF 6-THIOGUANINE

Maddocks, J. L., Dooley, T., Hallamshire Hospital, Dept. of Clinical Pharmacology, *Sheffield S10 2RX, England, United Kingdom*

OBJECTIVE: To devise a simple, rapid, specific and sensitive assay for measuring therapeutic concentrations of 6-thioguanine in plasma and cells and to conduct preliminary clinical studies.

APPROACH: To use a highly selective, solvent extraction procedure coupled with fluorimetric detection.

PROGRESS: A specific assay for 6-thioguanine in human plasma has been developed with a sensitivity of 5 ng/ml. An oral dose of 160 mg of thioguanine was administered to a patient with leukemia. A peak plasma concentration of 460 ng/ml occurred at 4 hours and by 6 hours it dropped to 160 ng/ml.

107. TIGHT-BINDING INHIBITORS OF ADENOSINE DEAMINASE

Baker, D. C., Murphy, J., Hawkins, L. D., University of Alabama, School of Arts & Sciences, Dept. of Chemistry, *Box 1937, University, Alabama,* 35486, United States of America

The proposed research involves the chemical synthesis and enzymological evaluation of certain nucleoside derivatives that are designed as transition state inhibitors of adenosine deaminase (ADA), the enzyme that is responsible for the in vivo degradation of a number of adenine nucleosides that are of interest in cancer chemotherapy. Within the past four years these potent inhibitors of ADA, such as covidarabine (CoV, 2'-dexycoformycin), have been shown to potentiate the effects of nucleosides such as ara-A(9-beta-D-arabinofuranosyladenine) on certain neoplasms, especially those forms of leukemia that are resistant to the more traditional modes of therapy. Drug combinations of certain adenine nucleosides (e.g., ara-A) with CoV have been suggested as possibly useful regimens for management of these leukemias in humans.

Specifically it is proposed that certain lead compounds, such as CoV, will be used as models on which to design analogs and explore structure-activity relationships for this new class of nucleosides, with the aim of establishing a clearer picture of the precise elements responsible for the potent inhibition exhibited by these inhibitors. In a practical sense, the possibility of synthesizing a simpler, more stable structure than the labile and expensive CoV, which would facilitate production and handling, is an attractive goal. Certain aspects of the medicinal chemistry of other less potent inhibitors (e.g., erythrohydroxynonyladenine, EHNA, and 9-(beta-D-ribofuranosyl-1-6-dihydro-6-hydroxymethyl) purine) will also be studied. The chemical synthesis will be conducted alongside an in-house enzyme-assay program that will ensure maximum biological feedback to the chemist.

108. MECHANISM OF ARABINONUCLEOSIDE METABOLISM IN HUMAN CELLS IN VITRO

Fridland, A., St. Jude Children's Research Hospital, Dept. of Biochemical & Clinical Pharmacology, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee,* 38101, United States of America

The objective of this proposal is to identify the metabolic pathways required for conversion of the naturally occurring toxic purine nucleosides, adenosine (Ado), 2'-deoxyadenosine (dAdo) and that of their pharmacologically active arabinonucleoside analogs, 9-beta-D-arabinofuranosyladenine (ara-A) and its 2-fluoro derivative, F-ara-A in cultured human leukemic lymphoblasts, termed CEM. The approach in these studies will be to isolate mutants from CEM cell cultures which have been selected for resistance to the toxic effect of either Ado or dAdo. The mutants resistant to Ado and dAdo will be tested for cross-resistance to the two selective drugs as well as to the arabinonucleosides to determine whether different metabolic pathways are required for activation of Ado and dAdo or the two analogs to their toxic metabolite.

The nature of the biochemical alterations that are responsible for the resistance of the CEM mutant lines to the various toxic nucleosides will also be determined. This will include determination of the kinase activity for phosphorylation of the various nucleosides in the wild-type and mutant CEM cells and the kinetic properties of the various enzymes with purine nucleosides. Completion of these studies will provide information on the relationship of various nucleoside kinases to purine ribo- and deoxyribonucleoside metabolism and their arabinonucleoside analogs in lymphoid cells. Ultimately information gained from this project should lead to more effective clinical use of these two chemotherapeutic agents.

109. CELL PROLIFERATION KINETICS IN HEMATOPOIETIC TUMORS

Clarkson, B. D., Fried, J., Hansen, H., Yen, A., Delmonte, L., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

The aim of the proposed work is to achieve a better understanding of the proliferative behavior and related properties of the neoplastic cells in different hematopoietic tumors. It is hoped that more complete information about cellular kinetics will permit not only formulation of more effective treatment schedules but will also lead to clearer definition of the fundamental abnormalities in the hematopoietic tumors and of the interrelationships between them.

Patients with hematopoietic tumors will be studied before, during and following chemotherapy, using autoradiographic and continuous flow microfluorometric methods, to determine the kinetic changes caused by different drugs and with the goal of devising improved treatment schedules.

Studies will also be conducted in vitro on established cell lines of human hematopoietic cells during their different growth phases and on fresh human normal lymphocytes and leukemia and lymphoma cells to determine the perturbations caused by different drugs and the influence of natural regulatory factors. Techniques are being developed to purify and isolate clonogenic cells from normal blood and bone marrow in order to characterize their properties and compare them with clonogenic cells derived from human hematopoietic tumors.

BIBLIOGRAPHIC REFERENCES: Cunningham, I., Gee, T., Dowling, M.D., Chaganti, R.S.K., Bailey, R., Hopfan, S., Bowden, L., Turnbull, A., Knapper, W., and Clarkson, B.: Results of Treatment of Ph' plus Chronic Myelogenous Leukemia with an intensive Treatment Regimen (L-5 Protocol). Blood 53: 375-395, 1979. Arlin, Z.A., Fried, J., and Clarkson, B.: Human Acute Leukemia. In: Flow Cytometry and Cell Sorting. (Mendelsohn, M.L., Melamed, M.R., and Mullaney, P., eds.), J. Wiley and Sons, Publishers, 1979, pp. 583-597.

110. ANTIMETASTATIC AND ANTITUMOR ACTION OF TRIAZENES, DIAZODERIVATIVES OF AMINO ACIDS AND PROTEOLYTIC ENZYME INHIBITORS

Giraldi, T., Baldini, L., Sava, G., Nisi, C., Bertoli, G., Bartoli Klugman, F., Universita degli Studi di Trieste, Inst. of Pharmacology, *I34100 Trieste, Italy*

OBJECTIVE: The aim of this research project is to develop selective antimetastatic agents (treatments), i.e. substances (of synthetic and natural origin) capable of inhibiting the specific processes leading to metastasis formation, thus preventing tumor spread. These agents might be employed as chemoprophylactic adjuvants for preventing metastasis formation in the period between tumor diagnosis and surgical or radiotherapeutic treatment. They might also be employed in leukemic patients, in order to prevent leukemic invasion of organs, such as the brain, having low accessibility to cytotoxic agents.

APPROACH: Imidazole and benzenoid dimethyltriazenes have been shown by us to cause selective antimetastatic effects in mice bearing Lewis lung carcinoma: neutral proteinase inhibitors are similarly active. The latter finding is in agreement with the literature data reporting high levels of proteinases in malignant tumors and suggesting their participation in the process of metastasis formation. The approach followed consists in the quantitative structure-activity relationship determination of antimetastatic properties of benzenoid dimethyltriazenes, diazoderivatives of aminoacids and other neutral proteinase inhibitors. These compounds are tested for inhibitory effects on primary tumor proteolytic activity, and the active ones are examined as prophylactic adjuvants in chemotherapy plus surgery survival time experiments.

PROGRESS: p-(3,3-dimethyl-1-triazeno) benzoic acid potassium salt and DTIC, without exerting any cytotoxic effect, inhibit metastasis formation in mice bearing Lewis lung carcinoma, preventing tumor cell entrance into the blood stream. These triazenes also increase life span of leukemic mice, without having antiproliferative effects on leukemic cells.

111. PHARMACOLOGY AND PHASE I TESTING OF ALPHA-2'-DEOXYTHIOGUANOSINE (ALPHAGDR)

LePage, G. A., Khaliq, A., University of Alberta, Cancer Research Unit, McEachern Laboratory, *Edmonton, Alberta, Canada*

OBJECTIVE: To determine the potential carcinostatic activity of alpha-TGdR in selected patients.

APPROACH: Biopsies of solid tumors and peripheral blasts from leukemias are assayed for ability to phosphorylate alpha-TGdR, an activation capacity that has been shown to be present in some tumors and not in normal tissues. Patients with tumors having high activity levels, where feasible, will be treated with alpha-TGdR at 1500 mg/m2/day x 10 in monthly courses.

PROGRESS: No evaluable patients, as yet. Assessment of the kinase level in tumors necessary to produce carcinocidal effects is being studied by assaying for kinase and conducting growth studies in vitro on human tumor cell lines.

112. CLINICAL PHARMACOLOGY OF INTRATHECAL METHOTREXATE

Bleyer, W. A., Hartmann, J. R., Chard, R. L., Opheim, K. E., Children's Orthopedic Hospital & Medical Center, Hematology & Oncology Division, *4800 Sand Point Way N.E., Box C-5371, Seattle, Washington*, 98105, United States of America

The goal of this project is to improve the therapeutic index of intrathecal methotrexate for the treatment of brain tumors, meningeal leukemia, and other neoplasms primary or metastatic to the central nervous system. The approaches that will be taken include 1) correlation of cerebrospinal-fluid antifolate concentrations with therapeutic and toxic effects, 2) identification of patient characteristics that influence the central-nervous-system pharmacokinetics of methotrexate, 3) Phase 2 and Phase 3 trials of intrathecal aminopterin, 4) pharmacological evaluation of the hyperbaric injection technic, 5) additional clinical experience with intraventricular chemotherapy via the Ommaya reservoir, and 6) the testing of new methods of central-nervous-system chemotherapy in murine and primate models. The latter will include evaluation of a variety of conditions on cerebrospinal-fluid methotrexate concentration: intravenous infusions of high-dose methotrexate, cranial irradiation, systemic and intrathecal probenecid administration, body position and hyperbaric (D10W-Trendelenberg) intralumbar chemotherapy. A primate model of methotrexate-induced leukoencephalopathy will be evaluated in order to determine what factors contribute to, prevent, or reverse the toxicity.

The ultimate objective is to eliminate the need for intrathecal methotrexate. This possibility will be explored by infusing very high doses of methotrexate, 33.6 gm/m2, intravenously for 24 hours periods, followed by citrovorum rescue. A prospective randomized trial is planned in patients scheduled to receive treatment for prevention of CNS leukemia.

BIBLIOGRAPHIC REFERENCES: Bleyer, W.A., and Koup, J.R.: Medication errors during intensive care. Am. J. Dis. Child. 133: 366-367, 1979. Pizzo, P.A., Poplack, D.G. and Bleyer, W.A.: Neurotoxicities of current leukemia therapy. Amer. J. Pediat. Hemat. Oncol. 1:27-140, 1979.

5. RADIOTHERAPY AND IMMUNOTHERAPY

113. ACUTE LEUKEMIA AFTER RADIATION AND/OR CHEMOTHERAPY

Rowley, J. D., University of Chicago, Pritzker School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

The summary for this project is under entry no. 73.

114. FACTORS AFFECTING LEUKEMIC TRANSFORMATION IN VIVO

Boggs, S. S., University of Pittsburgh, School of Medicine, Dept. of Radiology/Medicine, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

Therapy of leukemia is usually aimed at selective destruction of all malignant cells, permitting regrowth of surviving normal hematopoietic cells. Four acute lymphoblastic leukemia patients treated with whole-body irradiation and bone marrow transplantation relapsed with cytogenetic evidence of leukemia in donor cells. This strongly suggests a viral etiology for at least this form of human leukemia, and requires that the approach to treatment be rethought and adjusted to include not only abolishment of all existing malignant cells, but also prevention or minimization of subsequent transformation of normal cells.

The purpose of the present study is to use the AKR murine transplant model we have developed to delineate mechanisms involved in leukemic transformation in vivo. Transplantation of normal isogeneic and H-2 compatible allogeneic bone marrow cells into lethally irradiated leukemic mice and cytogenetic identification of leukemic cells in relapse should enable us to separate host and donor cell-related factors influencing transformation. The AKR strain of mouse has a very high incidence of spontaneous lymphatic (thymic) leukemia. Isogeneic AKR(R6.15)1Ald mice and H-2k histocompatibile allogeneic CBA mice with cytogenetic markers are available and AKR(R6.15)1Ald crosses have been made to produce F1 mice with markers. After lethal irradiation of preleukemic and leukemic AKR mice and injection of sufficient numbers of normal hematopoietic cells of a different cytogenetic type to prevent death due to hematopoietic depletion, frequency, latency and cytogenetic type of cells in leukemic relapse are determined. Experiments have shown that leukemic relapse and transformation of AKR donor cells occur very rarely and transformation of CBA cells occurs even more rarely. Experiments are described which are designed to determine whether the factors important in transformation are inherent in the donor cells and activated by transplantation or whether they are related to the host or both.

AKR(R6.15)1Ald spontaneously leukemic mice have been the origin of lines of transplantable tumors bearing chromosome markers. When transplanted into AKR mice, these tumors migrate to the lymphoid organs and grow to cause leukemia and death. Sister chromatid exchange rates assayed in mitotic cells from these leukemic mice will be used to determine damage and repair caused by therapeutic agents. (Text Abridged.)

115. MEAN MARROW DOSE AND 'LEUKEMIA DOSE' OF THE SWISS POPULATION (1978)

Poretti, G. G., Ionesco, F., Garavaglia, G., University of Bern, Dept. of Medical Radiation Physics, c/o Radiuminstitut, *Inselspital, CH3010 Bern, Switzerland*

OBJECTIVE: Calculation of the mean marrow dose and of the 'leukemia dose' of the Swiss population (1978-79).

APPROACH: The 'annual mean marrow dose of a population' can be calculated from the single doses received from each part of active bone marrow irradiated in the course of an X-ray examination and, as in the case of the genetically significant dose, from the demographic data. The annual mean marrow dose (1971) for the Swiss population was tentatively calculated using the values of the mean marrow dose per examination of the UK survey of 1957/58 and amounts to about 121 mrad. Barium meal contributes about 30% of the total; intravenous pyelography, barium enema, lumbar spine and mass miniature radiographies each account for about 10%.

PROGRESS: Experimental measures and calculation of the mean marrow dose of the Swiss population. Low dose radiation burden of a population in connection with the increase of the (myelotic) leukemia cases.

116. THYMIC RADIATION IN CHRONIC LYMPHOCYTIC LEUKEMIA (HUMAN)

Carpenter, J. T., University of Alabama in Birmingham, School of Medicine, Dept. of Medicine, *1919 7th Ave. S., Birmingham, Alabama*, 35233, United States of America

This is part of a broader project. A summary of this subproject is not available.

117. ACUTE MYELOID LEUKEMIA - IMMUNOTHERAPY WITH BCG AND IRRADIATED ALLOGENEIC AML CELLS VERSUS NO MAINTENANCE THERAPY (ABBREV)

Harris, R., Freeman, C. B., Zuhrie, S. R., Delamore, I., University of London, St. Mary's Hospital Medical School, Dept. of Medical Genetics, *Norfolk Pl., London W2 1PG, England, United Kingdom*

OBJECTIVE: To determine whether immunotherapy alone prolongs first remission length, increases reinduction rate and lengthens post-relapse survival.

APPROACH: Patients achieving complete remission with daunorubicin and cytosine and receiving six week consolidation with cyclophosphamide and 6-thioguanine are randomized to receive either immunotherapy alone with 10 to the 9th power irradiated allogeneic AML cells plus BCG or no further maintenance treatment.

PROGRESS: The median first remission length for 21 patients receiving immunostimulation is 35 weeks versus 21 weeks for 20 patients on no maintenance treatment which is significant (P less than 0.05).

118. AML IMMUNOTHERAPY AND ITS EFFECT ON SURVIVAL, REMISSION, IMMUNITY TO LEUKEMIA CELLS, AND COLONY STIMULATING ACTIVITY (ABBREV)

Reizenstein, P., Hast, R., Lantz, B., Anderson, B., Beran, M., Uden, A., Karolinska Sjukhuset, Division of Hematology, *S10401 Stockholm, Sweden*

OBJECTIVE: To confirm our earlier findings on efficacy of immunotherapy in accute myeloid leukemia (AML), and to identify its mechanism of action.

APPROACH: Leukemia patients in remission given chemotherapy plus immunotherapy (CIT) are compared to patients given only chemotherapy (CT). CIT with BCG is compared to CIT with BCG plus leukemia cells. Leukemia cells are characterized by measuring antigenicity, cloning capacity, peroxidase and terminal transferase content, Ia-antigens, C3 and Fc-receptors, and soluble cell surface antigens. Non-specific immunocompetence and specific immunity to leukemia cells are measured in vitro and in vivo. Cellular and immune characteristics are correlated to prognosis. Macrocyte function, including CSA product, is monitored.

PROGRESS: Survival, frequency of second remissions, and, surprisingly, remission duration are significantly increased in CIT-group. Non-specific immunocompetence is no higher in CIT than in CT-group; in remission both are normal. Spontaneous 'immunity' to leukemic cells (in vitro) and proliferation of autologous lymphocytes are found in 1/4 of patients, but these patients do not have a better prognosis than remaining 3/4. Nor is frequency or intensity of 'immunity' to leukemia cells increased by CIT. Nor could we show that increased phagocytic or fungicidal function of macrophages, or fewer infections during relapse, explained IT-effect. According to a preliminary study, stem-cell number and function in bone marrow during remission are also normal in both CIT and CT groups. Our future aim is to determine if IT stimulates CSA. This could explain longer remission duration and more second remissions in CIT-group.

119. STUDY OF THE POSSIBLE PREVENTIVE EFFECT OF BCG AGAINST CANCER IN ADULTS

Frappier Davignon, L., Lavergne, B., Institut Armand Frappier, Centre de Recherche en Epidemiologie et Medicine Preventive, *531 Blvd. des Prairies, Case Postale 100, Laval-des-Rapides, Quebec*, H7N 4Z3, Canada

Studies have shown that BCG may have a non-specific preventive effect against mortality due to leukemia in children aged 0 to 4 years. This cohort study aims to determine if BCG could have a preventive effect against cancer in adults by comparing mortality and morbidity from cancer of all types among vaccinated and unvaccinated nurses. Names and addresses of all nurses graduated in the province of Quebec between 1952 and 1967 were obtained. A questionnaire was sent to each. This questionnaire included questions on age, date of graduation, marital status, BCG vaccination status, names of diseases of all kinds diagnosed since graduation, date of the event, place of diagnosis and treatment, name of physician, smoking habits, number of pregnancies and abortions and finally name and cause of death of classmates known to have deceased since graduation. The BCG vaccination status was verified in the central BCG record of l'Institut Armand-Frappier. Information has been received from 12,856 nurses of a possible total of 21,000, and 453 deaths have been reported. These data will be analyzed, taking into consideration vaccination status, age and time since vaccination.

120. SPECIFIC IMMUNOTHERAPY WITH MONOCLONAL ANTIBODIES

Bast, R. C., Ritz, J., Knapp, R. C., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

Using somatic cell hybridization techniques, monoclonal antibodies have been prepared against two human malignancies, acute lymphoblastic leukemia (ALL) and ovarian carcinoma. Studies are proposed to examine the pharmacokinetics and toxicity of these reagents after intravenous or intraperitoneal infusion. Methods will be sought to utilize or to prevent antibody-induced modulation of antigens from the surface of ALL cells. Monoclonal antibodies will be used to eliminate leukemic cells from bone marrow before antigenic modulation occurs, facilitating effective autologous marrow transplantation. Attempts will be made to analyze the capacity of antibodies of different subclasses to activate cellular or humoral effector mechanisms. The immunostimulant C. parvum will be administered to augment cellular effector function for antibody dependent tumor cell lysis. These studies should help to provide a more rational basis for the use of monoclonal antibodies for serotherapy of human cancer.

121. TRANSFER FACTOR THERAPY IN LEUKEMIA AND IMMUNE DEFICIENCY DISEASES

Lampkin, B. C., Children's Hospital Medical Center, *3245 Burnet Ave., Cincinnati, Ohio*, 45229, United States of America

This is part of a broader project. A summary of this subproject is not available.

122. IMMUNOTHERAPY STUDIES - LEUKEMIA (HUMAN)

Henderson, E. S., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

This is part of a broader project. A summary of this subproject is not available.

123. CHEMOIMMUNOTHERAPY OF ACUTE MYELOCYTIC LEUKEMIA WITH MER

Cuttner, J., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

This is part of a broader project. A summary of this subproject is not available.

6. OTHER AND NON-SPECIFIC THERAPY

124. MEASUREMENT OF INTERFERON LEVELS AND SENSITIVITY OF LEUKEMIC BLASTS TO INTERFERON IN AML PATIENTS GIVEN INTERFERON I.V. (ABBREV)

Balkwill, F., Watling, D., Rohatiner, A., Imperial Cancer Research Fund, Epithelial Cell Growth Regulation Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

A phase 1 toxicity trial to test human lymphoblastoid (Nama 1 wa) interferon in the treatment of A.M.L. patients has recently started at the ICRF Medical Oncology Unit, St. Bartholomew's Hospital. In parallel to this, a collaborative project between laboratories at Lincoln's Inn Fields and laboratories at St. Bartholomew's Hospital has begun to investigate the pharmacokinetics and effects of this interferon in vivo and in vitro. A sensitive and fast bioassay for serum interferon has been developed which measures the inhibition of viral RNA synthesis 6 hours after injection. Using this method, we have established that the first trial patient attained high levels of serum interferon 30 minutes to two hours after intravenous injection. As further patients enter the trial, more pharmacokinetic studies will be possible.

A microculture system for the short term culture of leukemia cells has been developed (Balkwill and Oliver, International Journal of Cancer, 1977, 20, 500) and this assay is being used to determine the in vitro sensitivity to interferon of the pre-treatment bone marrow and peripheral blood leukemia cells of each trial patient. A study using the first patient has shown that inhibition of cell growth in vitro could be obtained with doses of interferon that were attained in vivo after intravenous injection.

In trial patients with relatively normal levels of peripheral blood lymphocytes, investigations into natural killer cell activity in pre-and post-interferon treatment blood will be carried out to see whether these doses of interferon can stimulate the host immune system.

125. INTERFERON FOR CMV INFECTION, LEUKEMIC RELAPSE AND GVHD

Meyers, J. D., Neiman, P. E., Thomas, E. D., Singer, J., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

Efficacy of human leukocyte interferon in the prevention of CMV infection, relapse of leukemia, and graft-versus-host disease after marrow transplant for acute lymphocytic leukemia in remission is being studied in a randomized protocol.

Initial studies have identified a dose that seems both to be safe and to have measurable biological effects when given every 3 days to marrow transplant patients. Preliminary analysis suggests, for example, that the natural killer (NK) activity of circulating lymphocytes is increased in treated patients.

Data on the clinical efficacy of interferon should be forthcoming in the next 1-2 years.

126. INTERFERON TREATMENT IN LEUKEMIA

Greenberg, P. L., Merigan, T. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Service, *3801 Junipero Serra Blvd., Palo Alto, California*, 94304, United States of America

Interferon inhibits normal and neoplastic cell proliferating in experimental animals and in man (in preliminary clinical trials). Alternative forms of treatment are needed for patients with chronic myeloid leukemia (CML) since no essential change in the natural history of the disease has occurred in the past 50 years. The median survival of these patients is approximately 3.5 years due to the 80% incidence of transformation into a refractory phase known as blast crisis. Concern has been raised as to whether potentially oncogenic drugs such as busulfan may contribute to the high incidence of transformation. No such association has been found with interferon. With this in view we plan to evaluate the effects of interferon on leukemic cell mass in vivo and in vitro.

To date no patient with CML has been studied due to lack of availability of interferon. We have recently submitted to the NCI a proposal to obtain interferon for a Phase I/II trial evaluating the drug in patients with CML.

127. TREATMENT OF PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA IN RELAPSE WITH HIGH DOSES OF THYROID HORMONES

Logue, G. L., Cohen, H. J., U.S. Veterans Admin. Medical Center, Dept. of Medicine, Hematology-Oncology Section, *508 Fulton St., Durham, North Carolina*, 27705, United States of America

Because of the relatively small number of patients with this disease seen by us, we have not been able to enter any new patients since the last progress report. Most of our recent patients have been older and, thus, unable to tolerate the toxic effects of high dose T3. We have amended this protocol to also include patients with inoperable advanced non-oat cell carcinoma of the lung. Because of the shortages in personnel, we have not initiated this project, but hope to do so in the future.

128. NITROUS OXIDE IN THE TREATMENT OF REFRACTORY ADULT LEUKEMIA

Van Echo, D. A., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medical Oncology Section, *Baltimore, Maryland*, 21201, United States of America

Prolonged inhalation of nitrous oxide for four or more days has been shown to lead to marrow aplasia. There are scattered reports of decrease in peripheral white counts in leukemic patients; however, there have not been any systematic clinical trials. This protocol is a Phase I evaluation of nitrous oxide in the treatment of adults no longer responsive to conventional anti-leukemic therapy. The objectives of this study are to determine the role of nitrous oxide in suppressing myelopoiesis and to determine the most efficacious way to administer this therapeutic modality.

Five patients have thus far been entered onto this study, receiving 6 separate treatments which will be evaluated. There were no effects in peripheral white counts or bone marrow cellularity in any•patient. Future plans are to use continuous exposures of nitrous oxide for up to 96 hours.

129. THYMECTOMY IN T-CELL LEUKEMIA

Reichlin, S., New England Medical Center Hospital, *171 Harrison Ave., Boston, Massachusetts*, 02111, United States of America

This is part of a broader project. A summary of this subproject is not available.

130. CHARACTERIZATION OF B CELL PRECURSORS IN REGENERATING BONE MARROW FOLLOWING TERMINATION OF ANTI-LEUKEMIA TREATMENT

Soothill, J., Rapson, N., Paolucci, P., University of London, Inst. of Child Health, Dept. of Immunology, *30 Guilford St., London WC1N 1EH, England, United Kingdom*

The object of the study is to investigate the effect of anti-leukemia treatment on cells of the B lymphocyte series, from the point of view of immunosuppression. Also, since it throws light on the physiology and proliferation control of these cells, which are involved in many cases of leukemia, it may throw light on the leukemic process itself. We wish to characterize the B cell precursors, which are present in raised percentages in regenerating marrow and ,which may differentiate in short-term culture. Antigens to be tested for will include Ia, ALL and tDT; these are selected because of their association with different maturational stages of lymphocytes.

131. EXPERIMENTAL BASES FOR A MOLECULAR APPROACH TO CANCER PROPHYLAXIS AND THERAPY FOR SOME TYPES OF HUMAN NEOPLASIA

Phillips, L. A., Kang, M. S., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Laboratory of Viral Carcinogenesis, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The goal of this project is to make possible a molecular approach to cancer prophylaxis and therapy for some types of viral neoplasia, especially human leukemia and cancer of the breast, where retrovirus information has been detected. Major findings to date are: (1) Poly(A), poly(C), and poly(G) sequences are present in all retrovirus RNAs examined. (2) Poly(U) sequences are absent in retrovirus RNA. (3) Poly(C) and poly(G) sequences present in retrovirus RNA are transcribed into complementary poly(dG) sequences and poly(dC) sequences respectively in subunit-length cDNA of retroviruses. (4) The 3'-terminal poly(A) sequences are not transcribed into poly(dT) sequences. (5) Few or no poly(C) and poly(G) sequences have been detected in the cellular nucleic acids from nonmalignant mammalian and human embryonic cells.

BIBLIOGRAPHIC REFERENCES: Phillips, L. A., Pang, R. H. L., Park, J. J., Hollis, V. W., Jr., and Famuyiwa, F.: Poly(U)-agarose affinity chromatography, specificity, sensitivity, selectivity, and affinity of binding. Prep. Biochem. 10, 11-26 (1980). Phillips, L. A., and Kang, M. S.: Structural components of retroviruses: viral RNA and DNA. In Phillips, L.A. (Ed.): Viruses Associated with Human Cancer. New York, Marcel Dekker Inc. 1980 (In Press).

132. IMMUNOCOMPETENT CELLS IN ACUTE LYMPHOCYTIC LEUKEMIA

Casper, J. T., Keller, R. H., Holcenberg, J. S., Merritt, W., Lauer, S. J., Medical College of Wisconsin, School of Medicine, Dept. of Pediatrics, *561 N. 15th St., Milwaukee, Wisconsin*, 53233, United States of America

The specific aims of this proposal are: 1) To determine if phenotypically distinct ALL blasts possess cell surface antigens which are also expressed by a cell subset of normal regenerating bone marrow (a putative stem cell population) and to compare these antigens with those on normal lymphoid cells. Cells from regenerating bone marrow will be obtained from patients in remission after anticancer treatment has been stopped. These bone marrow cells and cell subsets will be characterized by their membrane markers, surface antigens and functional properties. 2) To establish if cell surface phenotypes of normal lymphocytes, normal lymphoblasts and neoplastic lymphoid cells correlate with the biochemical and pharmacological characteristics of these cells. 3) To determine in children with ALL the kinetics of recovery of T lymphocyte subsets and their helper or suppressor role in regard to B cell function after cessation of therapy.

133. IN VITRO GRANULOPOIESIS AFTER ANTILEUKEMIC THERAPY

Dow, L. W., St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

134. THERAPY OF ACUTE LEUKEMIA OF THE ADULT (HUMAN, MAMMALS)

Burke, P. J., Johns Hopkins University, School of Medicine, Dept. of Medicine, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

This is part of a broader project. A summary of this subproject is not available.

135. THERAPY IN ACUTE MYELOGENOUS LEUKEMIA (HUMAN)

Schrier, S. L., Stanford University, School of Medicine, Dept. of Medicine, *Stanford, California*, 94305, United States of America

This is part of a broader project. A summary of this subproject is not available.

136. CANCER THERAPY - ACUTE LYMPHOCYTIC LEUKEMIA (HUMAN)

Henderson, E. S., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

This is part of a broader project. A summary of this subproject is not available.

137. TOTAL THERAPY OF ACUTE LYMPHOCYTIC LEUKEMIA

Aur, R. J., St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

138. TREATMENT OF LEUKEMIA

Hathaway, W. E., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Pediatrics, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

This is part of a broader project. A summary of this subproject is not available.

D. PROTOCOLS

139. ACUTE MYELOGENOUS LEUKEMIA IN ADULTS - TRIALS B-8, B-9 AND B-10

Bell, R., Cullen, M. H., Malpas, J. S., Lister, T. A., Paxton, A. M., Johnson, S. A., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Trial B-8. Entry to this trial closed in April 1978, and follow-up of the surviving patients continues. Thirteen patients are still alive with nine in continuous complete remission (five for more than three years). Trials B-9 and B-10. Since April 1978, 77 consecutive previously untreated adults have been treated with a combination of adriamycin, cytosine arabinoside and 6-thioguanine. Two schedules have been employed. B-9 comprises six cycles of cytosine arabinoside 200 mg/m2 for five days and 6-thioguanine 200 mg/m2 for five days with adriamycin being increased from 50 mg/m2 on the first cycle to 100 mg/m2 on the sixth to give a total dose of 450 mg/m2. B-10 also comprised six cycles; cycles 1 and 2 consisted of cytosine arabinoside 200 mg/m2 and 6-thioguanine 200 mg/m2 each for seven days, with cycles 3-6 having five days only. Each cycle contained adriamycin 75 mg/m2. No further therapy is given and the patients are followed monthly in the clinic.

Preliminary analysis suggests the following: 1. The response to initial therapy for patients under the age of 60 is higher in B-9 and B-8. 2. The duration of first complete remission is longer in B-10 than in B-8 although the period available for follow up is short. There was no statistically significant difference between the complete remission rates in B-8 and B-10.

B-9 continues; B-10 was stopped because of very severe early toxicity.

140. PHASE II STUDY OF ARABINOSYLADENINE-5'-PHOSPHATE (ARA-A-5'-P)

LePage, G. A., Khaliq, A., University of Alberta, Cancer Research Unit, McEachern Laboratory, *Edmonton, Alberta, Canada*

OBJECTIVE: To determine the efficacy of Ara-A-5'-P in the treatment of selected clinical cancers.

APPROACH: Samples of the malignant cells (biopsy, bone marrow, peripheral blasts of leukemias, as suitable) are incubated in a cell culture medium with tritiated thymidine and various levels of Ara-A. Measurements are made of the sensitivity of DNA synthesis in these cells, as measured by the incorporation of tritiated thymidine, to various levels of Ara-A. Patients so selected are treated once daily for 10 days by i.v. injection of Ara-A-5'-P at 1300 mg/m2. A course is given every 28 days.

PROGRESS: Of some 25 patients treated, 1 chronic myelogenous leukemia in blastic crisis, 1 non-Hodgkin's lymphoma, 1 ovarian carcinoma, 1 melanoma and 2 myelomas have shown objective responses. A correlation has been observed between sensitivity in the above test and clinical response.

141. TREATMENT OF ACUTE LYMPHOCYTIC LEUKEMIA (ALL) IN HEMATOLOGIC RELAPSE

Jimenez, E., Carrillo, J., Navarrete, M., Jimenez, R., Hospital Nacional de Ninos, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: To determine the effectiveness of vincristine (VCR), adriamycin (ADR), prednisone (PRED), Ara-C and methotrexate (MTX) in the reinduction of patients with ALL in hematologic relapse; also, to determine the effectiveness of VCR, ADR, purinethol (6MP), PRED and MTX administered over 5 days in 21-day cycles as a maintenance therapy during remission.

METHOD: Induction of remission: 1.5 mg VCR iv and 25 mg/m2 ADR; 40 mg/m2 PRED vo and 1 dose per week for 6 weeks and 12 mg/sq. m intrathecal MTX every 21 days. Seventh and ninth weeks: 300 mg/m2 iv ARA-C every 4 days, 4 doses.

MAINTENANCE: Tenth week: 2 mg/m2 iv VCR and 30 mg/m2 iv ADR, one dose, day one. Days 1 through 5, 225 mg/m2/day 6MP and 120 mg/m2/day PRED. This cycle is repeated every 21 days for 30 months, with intrathecal MTX administered every second cycle. Upon reaching a total dosage of 450 mg/m2 ADR, substitution will be made of 7.5 mg/m2/day oral MTX, days 1 through 5. (Translated)

142. CNS PROPHYLAXIS IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

Freeman, A. I., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

Fifty percent of children with acute lymphocytic leukemia (ALL) may now be 'cured.' However, CNS impairments are occurring in these long-term survivors. It is not clear whether these problems are secondary to the disease, or to the mode of CNS trial prophylaxis. Cancer and Leukemia Group B (CALGB) in three separate clinical trials (CLB Protocols No. 7111, No. 7411 and No. 7611) has compared cranial irradiation (RT) plus intrathecal (IT) methotrexate (MTX) with IT MTX alone. In an earlier study (CLB Protocol No. 6801) a comparison of IT MTX with no specific CNS prophylaxis was made. We have the unique capability of retrospectively evaluating the effect of CNS prophylaxis on large numbers of randomly treated patients. A pilot study to Protocol No. 761, conducted at Roswell Park Memorial Institue, also tested IT MTX.

We will employ standardized neurological tests, standardized psychological and psychometric tests, CAT scans, EEG's and endocrine evaluation. There will be central review of these tests with evaluators blinded to the CNS treatment regimen received. This study will be a retrospective analysis where patients will be evaluated with the test battery on one occasion (Protocols No. 6801, No. 7111, No. 7411, No. 7611 and No. 7611 - pilot study).

Approximately 150 disease-free children with ALL will be available for study for a two-year period. If both types of CNS prophylaxis are equally effective (i.e., cranial RT plus IT MTX versus intermediate dose MTX plus IT MTX), and one type results in a higher percentage of psychosocial and neurological sequelae, then this information is relevant to future trials and to recommendations for treatment in the community.

143. METHOTREXATE AT HIGH AND MEDIUM DOSES WITH RESCUE IN LYMPHOMA PATIENTS AND IN A NATIONAL LEUKEMIA TRIAL

Polli, E., Cortellaro, M., Periti, P., Djerassi, I., Universita degli Studi di Milano, Istituto di Clinica Medica IV, *Via F. Sforza 35, 20122 Milan, Italy*

The aim of this research project is to evaluate the efficacy of high doses of methotrexate (MTX) with N5-methyl-tetrahydrofolate (MTHF) rescue in cases of non-Hodgkin's lymphoma and acute lymphatic leukemia resistant to conventional chemotherapy. MTHF has been chosen in preference to leucovorin in hopes of improving the therapeutic index of the rescue program. The drugs are administered as follows: MTX, a 6-hour infusion of 0.5-1 g/m2 for leukemic patients and of 1-1.5 g/m2 for lymphoma patients every 7-10 days, followed by 15 mg/m2 MTHF every 6 hr, starting 2 hr after MTX infusion.

Different methodologies will be used to measure MTX and MTHF levels directly in patients' plasma.

The first part of our program has consisted of perfecting the methods to measure MTX and MTHF in plasma and urine. Some patients with lymphoma and leukemia have already been treated with high-dose MTX and MTHF rescue, and preliminary results have been published (Cortellaro et al., Chemioterapia Oncologica suppl. p. 311, 1978).

144. CONTINUOUS INFUSION VINDESINE - A PHASE II STUDY

Wernz, J. C., Muggia, F. M., Blum, R. H., Levin, M., Ballard, H., Hamilton, L., Dunleavy, S., Downey, A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1st Ave. at E. 24th St., New York, New York,* 10010, United States of America

The project to be undertaken has been designed to determine the efficacy of continuous vindesine infusion in the treatment of advanced solid tumors and lymphomas.

Procedures involved relating to human subjects are the administration of vindesine at a dose of 3mg/m2 by continuous 48 hour intravenous infusion to be repeated every 2 weeks. Vindesine is derived from the vinca alkaloid, Velban and is closely related to another, Oncovin (vinblastine). Vinblastine is useful in the treatment of various malignancies, chiefly in the treatment of Hodgkin's disease, and vincristine has shown effectiveness in several malignancies, especially acute lymphocytic leukemia. The antineoplastic activity of the vinca compounds has been related to the inhibition of microtubule formation in the mitotic spindle, a process that arrests dividing cells in metaphase. The binding of vinca alkaloids to tubulin may be their primary mode of action in causing cell death and peripheral neuropathy.

145. CLINICAL AND BIOLOGICAL ASPECTS OF A NEW TREATMENT FOR ACUTE NONLYMPHOCYTIC LEUKEMIA

Mandelli, F., Papa, G., Amadori, S., Isacchi, G., Alimena, G., Petti, M. C., Montuoro, A., Testa, M. G., De Felice, L., Di Lorenzo, A., Pasqueletti, D., Rosato, V., Universita degli Studi di Roma, VI Clinica Medica, Dept. of Hematology, *Via Lancisi 3, 00161 Rome, Italy*

PROTOCOL ANLL-79 UPDATE: As of December 31, 1979, 46 consecutive patients with acute nonlymphocytic leukemia (ANLL) have been treated according to the ANLL-79 protocol, which was activated on December 1, 1978. Forty-two consecutive untreated patients have been entered on the induction-phase of the protocol. Four additional patients were treated as per ANLL-79 prior to the protocol activation date; they all received for induction of remission the combination of cytosine arabinoside (CA) and rubidazone (RBD), the latter drug substituting for daunomycin (DNR). There were 24 males and 22 females. Median age 40 years (range 6-63); 8 patients were older than 55 years of age.

RESULTS OF THERAPY: Forty-six consecutive patients treated - 1 in induction, 2 not evaluable. 18/43 patients achieved C.R. (41.8%) - 1) CA-RBD: 2/4 (50.0%), 2) CA-DNR: 7/19 (36.8%), 3) DNR: 9/20 (45.0%). 19/43 patients died in induction (44.1%) - 1) CA-RBD: 1/4 (25.0%), 2) CA-DNR: 2/19 (10.5%), 3) DNR: 3/20 (15.0). 18 patients achieved CR (7 pre-protocol, 11 on protocol). The seven pre-protocol patients were treated early during the study with a different regimen of cytoreductive chemoradiotherapy: 5 initial marrow relapse (5, 12, 14, 15, 31 weeks); 1 initial cutaneous relapse (20 weeks); 1 died in CR (12 weeks). 11 responding patients on protocol: 1 died in CR (3 weeks.); 10 randomized (5 TBI, 5 no TBI); of these - 4 initial marrow relapse (TBI 2 (23, 26 weeks), no TBI 2 (17, 19 weeks); 6 patients remain in CCR (median 18-plus weeks).

TOXICITY: Profound myelosuppression was the principal toxic effect of induction therapy; in consequence, infectious episodes were responsible for the death of 19 patients. The toxicity of TBI was confined to marrow depression. Severe thrombocytopenia (less than 40,000/mm3) and/or neutropenia (less than 500/mm3) was commonly observed; however, major infectious or bleeding complications were never recorded. The nadir of peripheral blood cell counts was reached generally about 2-4 weeks after completing the course of TBI; platelets and granulocytes rose promptly following the nadir, returning to normal by the 6th-7th week. (Text Abridged.)

146. EVALUATION OF INTENSIFICATION AND MAINTENANCE PROGRAMS IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA

Pavlovsky, S., Sackmann Muriel, F., Grupo Argentino de Tratamiento de la Leucemia Aguda, *P. de Melo 3081, 1425 Buenos Aires, Argentina*

DESCRIPTION: A comparative Phase III trial designed to evaluate the usefulness of more frequent pulse of therapy during maintenance. Patients with acute lymphoblastic leukemia (ALL) are randomly assigned to receive pulse at 1, 2, 3, 4 and 6 and every 3 months therafter of: (1) vincristine and prednisone, or (2) sequential pulse with vincristine and prednisone or arabinosyl cytosine and cyclophosphamide successively.

This protocol was opened to all members of the group in January 1976. By June 1978 a total of 250 patients had been entered into this protocol, of whom 241 were evaluable. The results of induction treatment were as follows: 175 (86%) out of 203 children and 31 (82%) out of 38 adults achieved complete remission. According to the WBC count, of those children and adults who had at diagnosis a WBC count lower than 20,000, 91% and 89% achieved complete remission as compared to 75% and 75% of those with more than 20.000 WBC count (43%). From the group with sequential pulses at 18 months 90% and 40% respectively remain in complete remission. There is no statistical difference according to maintenance therapy; however, a highly significant difference (P less than 0.005) was observed according to the WBC count lower or higher than 20,000 in adults and children.

147. PHASE I STUDY OF 5-AZA-2'-DEOXYCYTIDINE IN CHILDREN WITH LEUKEMIA

Rivard, G. E., Momparler, R. L., St. Justine Hospital, Centre de Recherche Pediatrique, *3175 St. Catherine Rd., Montreal, Quebec,* H3T 1C5, Canada

There is need for new and more effective chemotherapeutic agents in the treatment of acute lymphoblastic leukemias that have become resistant to conventional drugs and for acute nonlymphoblastic leukmia, a disease that responds poorly to chemotherapy. Since 5-AZA-CdR is related to 5-a-acytidine, a drug that has already been shown to be clinically effective in acute leukemia of childhood, and since preliminary data indicate that 5-AZA-CdR is a potent antileukemic agent in animal and possibly in children, the potential usefulness of this agent should be investigated. Using an integrated approach where biochemical, cellular, animal and human studies are performed in the same institution by the same group, the antileukemic potential of 5-AZA-CdR can be rapidly evaluated and if this agent shows great potential, its introduction into a controlled Clinical Phase II study can be accelerated. Also, studying the mechanism of action of 5-AZA-CdR at the biochemical and cellular level with a variety of human leukemic cells and correlating those data with clinical evolution of patients will provide the rationale for the design of the most optimal dose schedules in possible future combination chemotherapy studies.

148. SEQUENTIAL THERAPY FOR INDUCTION AND MAINTENANCE OF REMISSION IN ACUTE MYELOBLASTIC LEUKEMIA

Pavlovsky, S., EppingerHelft, M., Grupo Argentino de Tratamiento de la Leucemia Aguda, *P. de Melo 3081, 1425 Buenos Aires, Argentina*

This is a Phase III study with the following objectives: 1) To confirm the usefulness of sequential induction treatment with daunorubicin, vincristine, prednisone followed by cytosine arabinoside-6-mercaptopurine in a new series of patients. 2) To compare the effectiveness of an intensive and intermittent maintenance treatment alternating monthly courses of cytosine arabinoside-6-mercaptopurine-CCNU with daunorubicin-vincristine-prednisone with or without adjuvant immunotherapy. 3) To study the effectiveness of prophylactic CNS leukemia treatment with 5 doses of intrathecal methotrexate early in remission.

THERAPEUTIC REGIMEN: INDUCTION: Daunorubicin (DNR) 1 mg/kg i.v. and vincristine (VCR) 1.5 mg/sq m i.v., both drugs at weekly intervals for 3 doses associated with prednisone (PRED) 40 mg/sq m daily orally for 14 days. Then: Cytosine arabinoside (C.Ara) 100 mg/sq m day i.v. plus 6-mercaptopurine (6MP) 2.5 mg/kg/day orally for 5 days until complete remission is achieved.

MAINTENANCE: C.Ara 100 mg/sq.m i.v. for 5 days plus 6-MP 2.5 mg/kg/day orally for 5 days plus CCNU 75 mg/sq m orally only once, alternating monthly with DNR 1 mg/kg/day i.v. plus VCR 1.5 mg/sq m/day, both drugs only for one dose, and PRED 40 mg/sq m/daily orally for 7 days.

PROPHYLACTIC CNS LEUKEMIA TREATMENT: During the first 5 weeks of maintenance the patients also receive intrathecal methotrexate (MTX) (12 mg/sq m) at weekly intervals.

IMMUNOTHERAPY: Half of the patients receive Corynebacterium parvum 4 mg (2 ml.) subcutaneously once a week between the maintenance courses.

PROGRESS: Out of 181 evaluable cases, 80 (44%) achieved complete remission. A total of 36 out of 45 randomized to chemotherapy relapsed, compared to 32 out of 35 of the chemoimmunotherapy group. Median duration of complete remission and survival was: for the chemotherapy group 8 and 15 months, for the chemoimmunotherapy group 5 and 10 months. This difference is not significant. Six patients (7%) had CNS leukemia at diagnosis. None had CNS leukemia relapse after prevention and IT methotrexate.

A progress report of this study was presented at the 14th ASCO meeting (page 402) 1978.

149. OMRF 7608 - PROTOCOL FOR ACUTE LYMPHOBLASTIC LEUKEMIA

Bottomley, R. H., Hussein, K. K., Murray, J. L., Grozea, P. N., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

OBJECTIVES: To improve remission rates and survival in adults with acute lymphoblastic leukemia (ALL).

PLAN: Patients with ALL are initially treated with vincristine, prednisone, adriamycin and L-asparaginase. Those who achieve complete remission are maintained on the cyclic regimen POMP-COAP-OPAL.

RESULTS: Only two V.A. patients have been treated on this protocol so far. Remission was achieved in both.

150. OMRF 74-02 - ACUTE NON-LYMPHOCYTIC LEUKEMIA (A-CAT)

Bottomley, R. H., Grozea, P. N., Hussein, K. K., Murray, J. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology & Oncology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

OBJECTIVES: To compare induction efficacy of (1) adriamycin plus OAP; (2) adriamycin plus Ara-C; (3) cyclophosphamide, adriamycin, Ara-C and thioguanine, in adults with acute non-lymphocytic leukemia. The best regimen will be the one which is most efficient in clearing the bone marrow of leukemic cells during the first and second courses, and thus improving the remission rate. To compare the effectiveness of 5-day maintenance - (1) OAP plus BCG; (2) Ara-C plus BCG; (3) Ara-C, thioguanine and BCG - in prolonging the duration of complete remission.

REMISSION INDUCTION: Eligible patients will be randomized to one of three treatment limbs, as follows: LIMB I: Adriamycin plus OAP; LIMB II: Adriamycin plus Ara-C; LIMB III: Adriamycin, Cytoxan, Ara-C and Thioguanine. A bone marrow aspiration (or a biopsy if a dry tap is obtained) will be carried out on day 18 to determine whether the bone marrow is cleared of leukemic cells and if marrow hypoplasia has been reversed, so that a further course can be instituted.

REMISSION CONSOLIDATION: Three consolidation courses will be administered at 14-day intervals, as follows: LIMB I: Ara-C - 100 mg/m2/day by 5 days by constant IV infusion; Prednisone - 50 mg b.i.d., PO by 5 days; Vincristine - 1 mg IV on day 1. LIMB II: Ara-C - 100 mg/m2 day by 5 days, by constant IV infusion. LIMB III: Ara-C - 100 mg/m2/day by 5 days, by constant IV infusion; Thioguanine - 2 mg/kg/day, PO, by 5 days. Dosage adjustments in Ara-C may be made when marrow hypoplasia occurs; the dose of subsequent courses can be reduced by 10%.

There is one veteran patient on this study at this time. This study is now closed to new patient entry.

151. OMRF 7505 - CHRONIC GRANULOCYTIC LEUKEMIA

Bottomley, R. H., Murray, J. L., Grozea, P. N., Hussein, K. K., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

OBJECTIVES: To determine if the combined addition of splenectomy and immunotherapy with BCG to intermittent busulfan therapy: a) delays the onset or reduces the incidence of blastic transformation, and b) improves the survival of previously untreated patients with chronic granulocytic leukemia, utilizing the results of SWOG study no. 545/546 as a historical control.

PLAN: The patient will take busulfan until the leukocyte count is between 5,000 and 9,000. One to three weeks after busulfan has been discontinued, the spleen will be removed if medically feasible. Two to three weeks after removal of the spleen, the patient will be treated with busulfan alternating with BCG scarification. When the white blood count is greater than 40,000, the busulfan will be taken by mouth daily until the white blood count is 9,000 or less; then, BCG will be given by scarification at weekly intervals until the white blood count is greater than 40,000. At this time, busulfan therapy will be resumed. This treatment will continue as long as the disease is responding, providing the patient has recovered from the side effects of the previous treatment.

This study is closed to new patient entry, with one V.A. patient remaining on the study.

152. OMRF 78-01 - PROTOCOL FOR TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

Bottomley, R. H., Grozea, P. N., Hussein, K. K., Murray, J. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

OBJECTIVES: To assess the response rate in chronic lymphocytic leukemia (CLL) to a combination of BCNU, Cytoxan, vincristine, and prednisone. To determine the value of the same regimen as maintenance therapy in patients who achieve complete and partial remissions.

PLAN: Eligible patients will be started on chemotherapy as follows: vincristine and BCNU I.V. day 1; Cytoxan P.O. days 1-4; prednisone P.O. days 1-7. Cycles of chemotherapy are repeated every three weeks. After a total of six courses, patient response is assessed. Those who achieve complete and partial response will continue on the same regimen for maintenance. Those patients who show no response and those with progressive disease will be removed from study.

There have been three patients registered on this protocol. This study is still active.

153. ANALYSIS OF COMPLEX DOSE RESPONSE SURFACES

Wampler, G. L., Virginia Commonwealth University, Medical College of Virginia, Dept. of Medicine, *1200 E. Broad St., Richmond, Virginia*, 23298, United States of America

Response surface methodology is being developed to analyze the results of combination chemotherapy experiments in mice bearing L1210 or P388 leukemia. Several different models of increasing complexity have now been successfully utilized including the logistic, a proportional hazard model and a non-proportional hazard model. Independent variables including drug dose, length of time between administrations of drugs and age of the treated tumor are being studied where the response variable is time to death. These studies not only provide more detailed information about the drugs used and their interactions but can serve as a guide for possible application of these methods to clinical combination chemotherapy or combined modality treatments. In that regard simulation studies are being undertaken to determine efficient design criteria, including how many groups and how many individuals in each group are required to give results, utilizing the minimum number of individuals for the entire investigation.

II. HODGKIN'S LYMPHOMA

A. DIAGNOSIS AND PROGNOSIS

154. STUDIES OF THE THERAPEUTIC EFFECT OF EARLY SPLENECTOMY AND CLINICAL SIGNIFICANCE OF THE IMMUNODEFICIENCY IN HODGKIN'S DISEASE (HD)

Holm, G., Mellstedt, H., Bjorkholm, M., Johansson, B., Askergren, J. N., Sundblad, R., Huddinge Sjukhus, Dept. of Clinical Immunology, *S14186 Huddinge, Sweden*

OBJECTIVES: 1. To evaluate the prognostic effect of early diagnostic splenectomy. 2. To evaluate the role of immunodeficiency in staging and prognosis. 3. To study the mechanism of immunodeficiency.

APPROACH: In January, 1973, a prospective randomized study was started including all HD patients with normal-sized spleen and uncertain prognosis. Clinical follow-up was undertaken in April 1979. All consecutive and previously untreated HD patients admitted to Radiumhemmet, Stockholm, since 1973 have been tested by skin tests and in vitro lymphocyte tests. A detailed evaluation of the immune status of patients, healthy relatives and healthy close contacts is being performed.

PROGRESS: 1. At the latest follow-up, 31 patients had been splenectomized (S-positive) and 36 had not (S-negative). After 40 months of observation there was no difference between the groups in terms of survival and the number of recurrences. However, relapses occurred earlier in the S-positive group. Pneumococcal septicemia was recorded in two S-positive patients. It is concluded that prognosis is not improved by diagnostic splenectomy in HD patients with uncertain prognosis treated with total nodal irradiation. 2. The lymphocyte deficiency measured as increased spontaneous and decreased mitogen-induced blood lymphocyte DNA synthesis is a strong predictor of poor prognosis. 3. The T-lymphocyte deficiency persists essentially unchanged during remission regardless of the type of treatment. It is present in healthy first degree relatives and husbands/wives of immunodeficient patients. It is assumed to be caused by environmental factors such as virus infection. Patients with active HD have serum factors associated to lipoproteins which inhibit lymphocyte stimulation. This may contribute to the profound immunodeficiency in patients with overt disease but does not seem to cause the persistent lymphocyte defect.

155. LAPAROTOMY AND SPLENECTOMY IN MANAGEMENT OF HODGKIN'S DISEASE (HUMAN)

Fischer, J. J., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

156. LONGITUDINAL STUDIES OF A POTENTIAL TUMOR MARKER IN THE SERUM OF PATIENTS WITH MALIGNANT LYMPHOMA

Tucker, D. F., Keen, J., Begent, R. H., Chester, K., Imperial Cancer Research Fund, Laboratory for Immunological Markers in Cancer, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Using a method developed primarily for the detection and characterization of circulating immune complexes in malignancy, analysis of material precipitating at low concentrations of polyethylene glycol by SDS-PAGE showed the presence of an extra protein band associated with lymphomas (ICRF Scientific Report 1978 - report 239). The serum factor had an apparent molecular weight of 23,000 daltons and is provisionally referred to as T23.

Preliminary data indicating that the appearance of T23 was disease-related have been followed by a more extensive investigation of the incidence of T23 in serial samples from 25 patients with Hodgkin's disease and 33 with non-Hodgkin's lymphoma.

T23 was detected in sequential samples from nine out of twelve patients with active Hodgkin's disease whereas its incidence was greatly reduced during response to chemotherapy (three out of thirteen) and in remission (three out of eleven). Of the three patients who had detectable T23 during remission, one relapsed within one month of the positive result, although the second has been clinically free of disease for one year. The third patient became positive three weeks after discontinuing chemotherapy but did not relapse in the ensuing two months.

A similar result was obtained from studies on non-Hodgkin's lymphoma with T23 present in the majority of patients with active disease (fifteen out of twenty-four), to a lesser extent during successful chemotherapy (six out of nineteen) and undetectable in any of seven cases in complete remission.

The correlation between active disease and presence of T23 indicates that measurement of this serum factor may be of use in the management of lymphomas. Investigation of its clinical potential is continuing.

157. STUDIES ON BIOCHEMICAL MARKERS IN HUMAN BREAST CANCER, LEUKEMIA AND LYMPHOMA

Skoog, L., Karolinska Sjukhuset, Dept. of Tumor Pathology, *S10401 Stockholm, Sweden*

The sum~~mary for this project is under entry no. 25.~~

158. RADIOISOTOPE IMAGING IN EARLY DIAGNOSIS AND MANAGEMENT OF MALIGNANT DISEASE AND TUMOR-SEEKING RADIOPHARMACEUTICALS (ABBREV)

Shanta, V., Lakshmanan, A. V., Rajalakshmi, P. K., Cancer Inst., Dept. of Radiotherapy & Physics, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: Prospective study of lymphomas using all available diagnostic evaluation methods, including 67Ga scanning.

APPROACH: The parameters studied are clinical parameters -hematology, marrow studies, biochemical investigations, lymphography, laparotomy and histology. All cases will be evaluated prior to treatment and on completion of treatment after a fixed time interval. The data will be analyzed and correlated to evolve criteria by which involvement of various sites and organs can be diagnosed using the various diagnostic methods listed above.

Sixty-five patients have been studied so far using mainly a 5-inch rectilinear scanner for the isotope investigation. The analysis is in progress and will be reported next year.

159. VERIFICATION OF THE VALIDITY OF THERORETICAL MODELS, PARTICULARLY OF COHEN'S MODEL FOR THE TIME-RELATED DOSE FRACTIONATION

Cavallo, V., David, V., Guerris, R., Marini, M., Porfiri, L. M., Universita degli Studi di Roma, Istituto Radiologia, *Policlinico Umberto I, Rome, Italy*

OBJECTIVE: Verification of the validity of theoretical models, particularly of Cohen's model for the time-related dose fractionation.

The purpose of this investigation is the quantitative estimation of opacized lymph nodes areas in the course of lymphography by means of liposoluble contrast medium. The study was conducted in a group of patients affected by Hodgkin's disease and non-Hodgkin's lymphoma; the control group was composed of patients affected by various diseases and considered negative, in part also during the laparoscopy. On the whole, 1813 normal lymph nodes, 1784 lymph nodes in patients affected by Hodgkin's disease and 1285 lymph nodes in patients affected by lymphoma were examined. Data are being analyzed. However, some preliminary results are available regarding (1) maximum values in cm2; (2) mean values; (3) standard deviation; and (4) meaning of the differences in mean values.

160. HODGKIN'S DISEASE IN DENMARK - THE DANISH HODGKIN STUDY GROUP, LYGRA

Kaae, S., Nordentoft, A. M., Radiumstationen i Aarhus, *c/o Kommunehospitalet, DK8000 Aarhus C, Denmark*

In 1967, a national clinical study group (LYGRA) was established with the following ojectives: to register prospectively all new cases of Hodgkin's disease (HD) in Denmark, to perform a central review of all diagnostic biopsies, to centralize the patients for uniform diagnostic procedures in a few centers and to carry out prospective randomized therapeutic trials. Since September 1971 all new cases of HD in Denmark have been referred to the participating departments, and we are now able to report data on all patients seen before July 1979.

As compared with the results of a very large number of studies of selected groups of patients our national study gives a reliable assessment of the therapeutic and prognostic outlook and the number and severity of complications for the average patient with HD.

During the last 8 years (1971-1979) all newly diagnosed previously untreated patients with Hodgkin's disease in Denmark have been centralized to uniform staging procedures and treatment. A total of 802 patients were registered, or 2 patients/100,000. Lymphangiography was performed in 708 patients (88%), and 437 patients (55%) underwent laparotomy with splenectomy. Treatment included radiotherapy, combination chemotherapy (MOPP or similar programs), and combined modality treatment. The overall 8-year actuarial survival for all stages combined was 66%, and relapse-free survival was 55%. 144 patients died of Hodgkin's disease, 23 from complications due to therapy and examination procedures, and 54 of unrelated causes. Survival was significantly better for patients without B-symptoms, and decreased gradually with advancing age. There was a strong correlation between unfavorable prognosis and advancing stage and/or histology, but mediastinal involvement had no influence upon the prognosis. Staging laparotomy was associated with 4 deaths due to infection, and splenectomy with 10 cases of severe pneumococcal infections, 4 of which were fatal. Fatal complications due to subsequent treatment included 2 cases of cardiac arrest following mantle-field irradiation and 3 cases of hemorrhage or sepsis following chemotherapy. Five cases of acute myeloid leukemia were observed.

161. IMMUNODIAGNOSIS OF LYMPHOMAS

Udayachander, M., Meenakshi, A., Michael, A., Muthiah, R., Cancer Inst., Dept. of Biochemistry, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: To facilitate the diagnosis of lymphomas in asymptomatic stage. The presence of a circulating lymphoma-associated antigen (LAA) has been demonstrated only in lymphoma patients by various immunological methods such as agar gel diffusion, immunoelectrophoresis and counter-electrophoresis. So far the sera of 152 normals, 496 cases of various types of cancers and 213 cases of confirmed lymphomas have been tested by these methods. These studies have revealed that a specific LAA anti-LAA system is possibly operative in lymphoma patients. At present this immunodiagnostic test is routinely employed to screen patients with such symptoms as low-grade fever, general debility and generalized lymphadenopathy. This study has shown promising results in that in 8 cases, the LAA test was reactive at the time of presentation when the histopathological diagnosis was inconclusive due either to the lack of representative specimens or to the non-availability of a sizable lymph node. In such cases, the histopathology later became confirmatory.

162. HODGKIN'S DISEASE IN NIGERIAN AND AMERICAN CHILDREN

Olisa, E. G., Williams, A. O., University of Ibadan, *Bauchi Rd., Jos, Nigeria*

The histological classification of Hodgkin's disease in Nigerian and American children is still being studied. Materials were collected from Ibadan University Teaching Hospital and Murtala Mohammed Hospital, Jos, both in Nigeria, and a few cases were obtained from Howard Univeristy Children's Hospital in Washington D.C., U.S.A. The American cases are 150 in number, whilst the number from Nigeria is 84. Collection continues. The natural history and histological patterns of the disease are being studied in relation to granulomatous infections, in particular tuberculosis and leprosy.

163. CHILDHOOD ENVIRONMENT AND HODGKIN'S DISEASE

MacMahon, B., Swanson, G. M., Evans, A. S., Long, J., Gutensohn, N., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The objectives of this study are: 1) To evaluate the hypothesis that risk of Hodgkin's disease is a function of factors in childhood environment which inhibit infectious transmission: in particular, family size, birth order and social class. 2) To re-evaluate the association of tonsillectomy and risk of Hodgkin's disease. 3) To evaluate occupational exposures and risk of Hodgkin's disease. 4) To establish a serum bank. In part I of the study, conducted in the Boston and Worcester metropolitan areas, essentially all incident cases of 54 month period will be identified. Controls will include siblings of cases as well as persons selected by a random process from the general population. Information will be gathered by home interview; blood specimens will be obtained from cases and sibling controls. Part II will be conducted by mail questionnaire in the Detroit metropolitan area. A similar case series will be identified and their siblings used as controls.

B. RADIOTHERAPY

164. RADIATION-RELATED THYROID DYSFUNCTION IN HODGKIN'S DISEASE

Schimpff, S. C., Wiernik, P. H., Salvatore, P., Wiswell, J. G., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Infection Research, *Baltimore, Maryland*, 21201, United States of America

Late complications in the treatment of Hodgkin's disease with radiation therapy are increasingly being recognized. Thyroid dysfunction following irradiation is one such complication which has not been widely recognized, probably because of the subtle clinical nature of minor thyroid hormone imbalance. In addition, it has long been thought that the thyroid was relatively resistant to radiation therapy. Two hundred thirty-two patients with Hodgkin's disease followed at the BCRP have been evaluated for post-therapy thyroid dysfunction. Forty-one percent of those with mantle radiation therapy had an elevated TSH, but normal T4; however, an additional 25% had an elevated TSH plus a depressed T4. Thus, 66% of 169 patients had evidence of thyroid dysfunction following mantle radiation therapy. Since thyroid hormone replacement is simple, inexpensive and usually without major side effects if properly monitored, it is reasonable in light of the foregoing to place all patients with an elevated TSH on thyroid replacement therapy regardless of whether or not they are chemically hypothyroid.

BIBLIOGRAPHIC REFERENCES: Schimpff, S.C.: Carcinoma of the thyroid. In Aisner, J., and Chang, P. (Eds.): Advances in Cancer Treatment Research. The Netherlands, Martinus Nijhoff, Publ., 1980, pp. 88-102. Schimpff, S.C.: Hormonally active tumors. In Lichtman, M.A., and Wiernik, P.H. (Eds.): The Science and Practice of Clinical Medicine. New York, Grune and Stratton, 1980 (in press).

165. LATE CARDIAC EFFECTS OF THERAPEUTIC MEDIASTINAL IRRADIATION

Gottdiener, J. S., Katin, M. J., Borer, J. S., Bacharach, S. L., Green, M. V., Lipson, L. C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Heart, Lung & Blood Inst., Clinical Physiology Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The late cardiac effects of anterior mediastinal irradiation were assessed in 15 patients, 5-15 years after radiation therapy for Hodgkin's disease. Diminished left ventricular ejection fraction (determined by ECG gated Tc99m left ventricular cineangiography) with exercise was present in 1/15 (33%) of patients; average ejection fraction at exercise was also below normal for the group. Pericardial effusion on echocardiogram was present in 40% of patients. Asymptomatic impairment of systolic left ventricular function and pericardial effusion may be commonly present many years after mediastinal irradiation for Hodgkin's disease.

166. HODGKIN'S DISEASE, STAGE IIB, IIE, IIS, IIIA, IIIB (AGE 15-65 YEARS) CONTROLLED STUDY OF COMBINED TREATMENT - CHEMOTHERAPY AND RADIOTHERAPY

Banfi, A., Biasi, Buraggi, Guindani, Pagnoni, Recchione, Rodari, Santoro, Spinelli, Villani, Volterrani, Zucali, Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVE: Hodgkin's disease, stage IIB, IIE, IIS, IIIA, IIIB - a) Comparative evaluation of the effectiveness of two combined treatments: 1) 3 cycles MOPP plus RT plus 3 cycles MOPP; 2) 3 cycles ABVD plus RT plus 3 cycles ABVD. b) Systematic evaluation of the possible iatrogenic damage to the following organs: gonads, lung, heart and pericardium, thyroid, kidney, salivary glands, bone marrow.

APPROACH: Age of eligible patients - 15-65 years. Patients are stratified according to the following parameters: stage, modalities of staging, and histologic subtype. The patients are then randomized to treatment 1 or 2. For the alleviation of iatrogenic damages clinical tests are performed before the beginning of treatment, after the first three cycles of CT, at the end of RT, at the completion of the whole treatment and during the following three years, at 6-month intervals.

PROGRESS: Thirty-four patients were entered on the two combined treatment protocols according to the protocol. Only 16 were submitted to clinical tests for the alleviation of the iatrogenic damage.

167. CANCER RISK AFTER IRRADIATION AND/OR CHEMOTHERAPY

Schottenfeld, D., Tan, C. T., Hajdu, S. I., Mohan, R., Reid, A. M., Brody, R. S., Memorial Sloan Kettering Cancer Center, Dept. of Medicine, *1275 York Ave., New York, New York,* 10021, United States of America

The primary objective is to determine whether Hodgkin's disease patients are at increased risk of developing multiple primaries following varying doses and/or ordered sequences of radiation therapy and chemotherapy (given singly or in combined regimes). Histopathological classification of Hodgkin's disease and the extent of disease at first treatment will be studied in relation to the patterns of second primary cancer occurrence by organ site and histopathology. Quantitative estimation of radiation exposure will consider the total dose of radiation delivered, the energy used, the volume of tissue irradiated and the fractionation pattern of the treatment. Multiple entry and exit life tables will be used to characterize temporal patterns of exposure to different treatments, either alone or in combination. Patients will be withdrawn as transfers (not losses) from one treatment classification to another according to interval following first treatment. Internal historical cohorts of patients having recieved different doses and combinations of therapy will be identified and followed longitudinally to contrast their subsequent multiple primary cancer experience. Risk of new primary cancer among 1,500 Hodgkin's disease patients who have been intensively treated with potentially carcinogenic drugs, such as alkylating agents and steroid hormones, should identify carcinogenic doses or treatment combinations.

168. COMBINED CHEMOTHERAPY AND RADIOTHERAPY FOR HODGKIN'S DISEASE (HUMAN)

Schnipper, L., Beth Israel Hospital, *330 Brookline Ave., Boston, Massachusetts,* 02215, United States of America

This is part of a broader project. A summary of this subproject is not available.

169. RADIOTHERAPY, CHEMOTHERAPY OR COMBINED MODALITY TREATMENT FOR EARLY HODGKIN'S DISEASE

Wiernik, P. H., Young, R. C., Glatstein, E., Slawson, R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland,* 21201, United States of America

Eighteen patients with stage II-IIIA1 Hodgkin's disease have been randomly allocated to receive either radiotherapy, MOPP chemotherapy, or the combination of the two modalities for treatment. The study is designed to determine the best therapy for patients with early stage Hodgkin's disease. This study is an ongoing one and represents a long-term commitment whose objective is to precisely define optimal treatment for this group of young individuals with a malignant disease. In addition, the study asks whether the treatment of Hodgkin's disease might be simplified from the standpoint of expense, morbidity, and comfort by minimizing treatment for subgroups of patients who require less therapy. The long-term consequences of effective therapy will be evaluated in this study over a period of years.

170. CANCER RISK AFTER IRRADIATION AND/OR CHEMOTHERAPY

Schottenfeld, D., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York,* 10021, United States of America

The primary objective of this research is to test the hypothesis of whether Hodgkin's disease patients are exposed to an increased risk of the development of subsequent multiple primaries by the various intensities and/or ordered sequences of radiation therapy and chemotherapy (given singly or in combined regimens) which have served as therapeutic approaches to the management of Hodgkin's disease.

Histopathologic classification of Hodgkin's disease and the extent of disease involvement at the time of first treatment will be studied in relation to the patterns of second primary cancer occurrence by organ site and histopathology.

171. NO. 7551 - COMBINATION CHEMOTHERAPY AND RADIOTHERAPY FOR STAGE IV HODGKIN'S DISEASE, NO PRIOR TREATMENT

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York,* 14215, United States of America

This study compares combination chemotherapy with CCNU, vinblastine, procarbazine and prednisone given continuously with the combination drugs given with radiation therapy in patients who present primarily with advanced Stage IV Hodgkin's disease. The study is continuing. One patient has been entered at the VA Medical Center. The patient tolerated the treatment well, however, relapsed after three courses of chemotherapy. He has subsequently received radiation alone and remains free of disease. Final results are not available as this is part of a larger study.

172. SECOND CANCERS IN PATIENTS WITH HODGKIN'S DISEASE

Hutchison, G. B., Boivin, J., Hellman, S., Aisenberg, A. C., Desforges, J. F., Kim, T. H., Methot, Y., Bachand, A., Lavallee, R., Tawil, E., Thuot, C., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts,* 02115, United States of America

OBJECTIVES: To determine the long-range hazard, in terms of carcinogenesis, of radiotherapy and of chemotherapy used in treatment of Hodgkin's disease.

SPECIFIC AIMS: (1) To determine the incidence of second primary malignancies in patients treated with modern modalities for primary Hodgkin's disease. (2) To determine the variation in incidence of second primary malignancies by modality of therapy for primary Hodgkin's disease, comparing: (a) non-intensive radiotherapy; (b) intensive radiotherapy; (c) non-intensive chemotherapy; (d) intensive chemotherapy. (3) To determine the variation in incidence of second primary malignancies by time since initiation of therapy for Hodgkin's disease. (4) To determine the distribution by organ site of second primary malignancies.

METHODS: A cohort study is being conducted, using retrospective data on Hodgkin's disease patients diagnosed in 1940 to 1975 and followed to 1976 or death before 1976 and using prospective data on these same patients followed to 1980 and on patients newly diagnosed after 1975 and followed to 1980. It is planned to enroll 1000 patients diagnosed in 1940-69 and 1000 patients diagnosed in 1970-78. Patients with Hodgkin's disease are ascertained through registration records of four large cancer treatment centers.

173. NO. 7751 - POOR RISK PATIENTS, STAGE I AND II HODGKIN'S DISEASE

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study is designed to determine if involved field radiotherapy plus six cycles of chemotherapy with CCNU, Velban, procarbazine and prednisone prolongs the total duration of remission as compared to combination chemotherapy alone in patients with poor prognosis Hodgkin's disease. It will also determine whether combination chemotherapy alone, as compared to involved field radiotherapy, significantly decreases the morbidity or mortality and whether disease relapse patterns (either inside or outside irradiated fields) are different. This is part of a larger study and no results are available at this time.

No patients have been entered on this study.

174. KARYOTYPIC ANALYSIS IN RELATION TO CANCER SUSCEPTIBILITY, ETIOLOGY AND THERAPY

Watt, J. L., Brown, T., University of Aberdeen, Cytogenetics Lab., Dept. of Genetics, *Foresterhill, Medical School Bldgs., Aberdeen AB9 2ZD, Scotland, United Kingdom*

OBJECTIVE: The project is designed to evaluate the use of modern cytogenetic parameters in measuring susceptibility to cancer by comparing patients with confirmed double primary cancer with both 'single cancer' and 'asymptomatic' controls. A further aim of the project is to monitor patients with Hodgkin's disease undergoing modern radiotherapy/chemotherapy in an attempt to detect those at greatest risk of developing a treatment-induced, second malignancy. It is hoped that the study will aid early diagnosis of specific iatrogenic neoplasms and perhaps even provide a means of estimating predisposition to cancer in general, thus granting time for evasive action.

APPROACH: Chromsomes from blood and/or bone marrow cultures will be examined. Prometaphase karyotypes will be analyzed by G, and sequential C-banding and the rate of sister chromatid exchange will be estimated using a harlequin staining method. Photographic records of all chromosome analysis will be kept.

175. CHEMOTHERAPY AND LOW DOSE RADIOTHERAPY IN HODGKIN'S DISEASE (HUMAN)

Prosnitz, L., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

176. STUDIES IN THE DOSIMETRY OF IRREGULARLY SHAPED RADIATION FIELDS

Viswanathan, K. S., Lakshmanan, A. V., Cancer Inst., Dept. of Physics, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: To evaluate dose distribution in irregularly shaped fields.

APPROACH: The modern high energy radiation treatment of Hodgkin's disease uses large fields of about 40 by 40 cm with lead protection for shielding healthy areas of lung and other similar areas. Studies are in progress using an Alderson-Rando tissue-equivalent phantom and LiF-100 thermoluminescent dosimeter. A special geometric cutting machine has been designed to cut out the irregular field in thermal sheath material. A low melting alloy (Bi, Cd, Sn and Pb) with a melting point of 80 degrees C is employed to make a radiation shield for the individual patient.

C. CHEMOTHERAPY AND IMMUNOTHERAPY

177. HODGKIN'S DISEASE - COMBINATION THERAPY FOR RELAPSE FOLLOWING RADICAL RADIOTHERAPY

Timothy, A., Sutcliffe, S. B., Wrigley, P. F., Jones, A. E., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The results of mustine, vinblastine, procarbazine, prednisolone (MVPP) combination chemotherapy for relapsed Hodgkin's disease in 33 patients who were treated initially by definitive radiotherapy are analyzed. Twenty-three of 27 who received chemotherapy at first relapse achieved complete remission; 20 of these remained at remission at periods of 13-96 months (median 53 months) from treatment. Six patients were retreated by irradiation at first recurrence and all suffered further relapse within 14 months. Only three of this group achieved complete remission with subsequent chemotherapy. The results of radiotherapy for early stage Hodgkin's disease are improving now that certain presentations are recognized to be associated with high risk for relapse when treated by irradiation alone. The high rate of complete remission obtained with MVPP in patients with recurrence after radiotherapy suggests that chemotherapy may reasonably be withheld in the initial management of localized disease, thus reducing the risk of iatrogenic complications associated with combination therapy.

178. HODGKIN'S DISEASE, STAGE IIB, IIE, IIS, IIIA, IIIB (AGE 15-65 YEARS) CONTROLLED STUDY OF COMBINED TREATMENT - CHEMOTHERAPY AND RADIOTHERAPY

Banfi, A., Biasi, Buraggi, Guindani, Pagnoni, Recchione, Rodari, Santoro, Spinelli, Villani, Volterrani, Zucali, Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

The summary for this project is under entry no. 166.

179. NO. 7551 - COMBINATION CHEMOTHERAPY AND RADIOTHERAPY FOR STAGE IV HODGKIN'S DISEASE, NO PRIOR TREATMENT

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

The summary for this project is under entry no. 171.

180. RADIOTHERAPY, CHEMOTHERAPY OR COMBINED MODALITY TREATMENT FOR EARLY HODGKIN'S DISEASE

Wiernik, P. H., Young, R. C., Glatstein, E., Slawson, R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

The summary for this project is under entry no. 169.

181. SECOND PRIMARY MALIGNANCIES FOLLOWING RADIOTHERAPY OR CHEMOTHERAPY OR BOTH FOR HODGKIN'S DISEASE

Hutchison, G. B., Boivin, J. F., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The objective is to determine whether intensive radiotherapy or chemotherapy or their combination used in management of Hodgkin's disease is the cause of an increased incidence of secondary primary malignancies within 20 years after exposure. If an increase is found, it is desired to identify the details of the exposure responsible, the time relationships of the effect, and the spectrum of types of second malignancy. Approximately 2,000 patients with Hodgkin's disease treated in 1960 or later will be enrolled and followed for incidence of second malignancies. Patients will be ascertained through the collaboration of approximately 10 clinical centres in the United States and Canada. The study is planned as an independent test of the hypothesis derived from observation made at the National Cancer Institute, U.S.A., of an increased incidence of the total group of all malignancies. This increase is approximately 3-fold in patients given extensive chemotherapy or intensive radiotherapy and may be severalfold greater in patients given intensive courses of either therapy after relapse following an intensive course of the other therapy.

182. CANCER RISK AFTER IRRADIATION AND/OR CHEMOTHERAPY

Schottenfeld, D., Tan, C. T., Hajdu, S. I., Mohan, R., Reid, A. M., Brody, R. S., Memorial Sloan Kettering Cancer Center, Dept. of Medicine, *1275 York Ave., New York, New York*, 10021, United States of America

The summary for this project is under entry no. 167.

183. HOST DEFENSE

Souhami, R. L., Babbage, J., Addison, I. E., Gandossini, M., Imperial Cancer Research Fund, Tumor Immunology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

In the last three years we have made serial assessments of host defense functions in patients undergoing chemotherapy for Hodgkin's disease. The aim of the study has been to find out if host defense measurements can predict the occurrence of clinical infection. We have measured numbers of blood lymphocytes and monocytes during MOPP chemotherapy and at the same time have determined the migratory, phagocytic and candidacidal activity of both neutrophils and monocytes. The measurements have been made on days 0, 7 and 14 of each chemotherapy cycle and patients have been studied over many months. The study is the first to adapt a multifactorial approach to host defense measurement and to use a homogeneous clinical population with a defined chemotherapy regimen.

The results have shown that lymphopenia is a regular feature of chemotherapy with a tendency for this to lessen with later cycles of drugs. Many patients developed impaired neutrophil and monocyte function, these abnormalities being more marked in later cycles. Control hospitalized patients did not show functional defects. Six episodes of infection occurred with a marked tendency for the infected patients to have simultaneous depression of cell numbers and function during the cycle in which the infection developed. On the other hand, there was no set of abnormal host defense parameters that always predicted infection.

184. CHROMOSOME STUDIES IN PATIENTS WITH THERAPY INDUCED REMISSION OF LYMPHOMA

Garson, O. M., Cooper, I. A., Ding, J. C., Schwarz, M., University of Melbourne, St. Vincent's Hospital, Cytogenetic Unit, *Fitzroy, Victoria 3065, Australia*

OBJECTIVE: To investigate the chromosome constitution of bone marrow cells and blood lymphocytes in patients with Hodgkin's and non-Hodgkin's lymphoma who have achieved remission following combined chemotherapy and irradiation, to see if abnormal clones are present.

APPROACH: In recent years the prognosis of patients with lymphoma has improved greatly with the use of intensive treatment usually combining irradiation with chemotherapy. However, a significant number of such patients have developed acute non-lymphoblastic leukemia as a terminal event.

This study is being undertaken to see if chromosome damage, including the production of abnormal cytogenetic clones, may be produced by this therapy and persist in the marrows of some patients. It is initially a pilot study which will be extended if significant results are obtained.

185. PRENATAL EVENTS AND CANCER RISK IN THE OFFSPRING

Dukkers van Emden, D., Koppe, J. G., Peters, G. Universiteit van Amsterdam, Dept. of Neonatology, *Spui 21, Amsterdam, Netherlands*

The objective is to examine the relationship between use of anti-epileptic drugs or viral infection during pregnancy and cancer risk in the offspring. A follow-up study has been done of the outcome of 249 pregnancies in epileptic women undergoing treatment with anticonvulsants. The children were born between 1963 and 1977. Three children were stillborn, nine died subsequently. Postmortem examination in six cases showed multiple congenital abnormalities, no signs of malignancy. In the remaining group of 237 children, one boy, born in 1966, developed Hodgkin's disease (stage I) in 1973. His mother had used phenytoin, phenobarbital and primidone in high dosages during the entire pregnancy. No other malignancies were found in the group.

186. VINDESINE IN THE TREATMENT OF ADVANCED CARCINOMA OF THE LUNG, LYMPHOMA, METASTATIC MELANOMA, AND BREAST OR SOLID TUMORS

Kramer, B. S., Weiner, R. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Gainesville, Florida*, 32601, United States of America

Between 11/1/79 and 11/31/80, a total of 14 patients were entered onto this study. They demonstrated a variety of malignancies, i.e. melanoma, non-oat cell lung carcinoma, leukemia, esophageal carcinoma, and squamous cell carcinoma. Side effects of mild neutropenia, malaise, anorexia, jaw pain, and paresthesias occurred in many of the patients. All reactions were anticipated and reversible with termination of the drug. There were no treatment related deaths.

187. IMMUNOLOGIC ASPECTS OF CANCER

Fisher, R. I., Vanhaelen, C., Mann, D., Jaffe, E., Krizan, Z., Bostick, F., Greene, M., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medicine Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Recent studies in this laboratory have suggested that patients with Hodgkin's disease may have significant abnormalities of immune function unassociated with the presence of active disease. Assays of non-specific immunity are abnormal in patients with Hodgkin's disease cured by MOPP chemotherapy. These abnormalities cannot be attributed to the chemotherapy since they are not present in patients with diffuse histiocytic lymphoma cured by similar chemotherapy regimens. T lymphocytes in both untreated and cured patients with Hodgkin's disease have increased sensitivity to suppression by normal immune regulatory cells. This has been shown for both a macrophage suppressor cell and a T cell suppressor induced by concanavalin A. Both suppressor systems operate independently of prostaglandin E. A new serologic specificity closely linked to the HLA-Dr locus has been observed in cured Hodgkin's patients. Studies are in progress to define the genetics of these immune abnormalities by studying families of affected patients.

BIBLIOGRAPHIC REFERENCES: Fisher, R.I., Mandell, G.L., Bostick, F., McMenamin, M.G., and Anderson, T.: Chlorozotocin, an antitumor agent lacking bone marrow toxicity at therapeutic doses: Effects on lymphocyte subpopulations in mice. Clin. Exp. Immunol. 39: 416-425, 1980. Fisher, R.I., DeVita, V.T., Bostick, F., Vanhaelen, C., Howser, D.M., Hubbard, S.M., and Young, R.C.: Persistent immunologic abnormalities in long term survivors of advanced Hodgkin's disease. Ann. Intern. Med. 92: 595-599, 1980.

188. DISTRIBUTION AND FUNCTION OF LYMPHOID SUBPOPULATIONS IN ACUTE LYMPHOBLASTIC LEUKEMIAS AND LYMPHOMAS

Sen, L., Estevez, M. E., Finiasz, M., Diez, R., Guintoli, J., Instituto de Investigaciones Hematologicas, Depto. de Microbiologia, *Pacheco de Melo 3081, 1425 Buenos Aires, Argentina*

The summary for this project is under entry no. 84.

189. GLUCOCORTICOID RECEPTORS IN ADULT MALIGNANT LYMPHOMA

Bloomfield, C. D., Smith, K. A., Munck, A., Peterson, B. A., Gajl Peczalska, K. J., Frizzera, G., McKenna, R. W., Goldman, A., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Medicine, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

Glucocorticoids are included in most drug regimens used for malignant lymphoma although they add no significant antitumor effect in many patients and often cause significant toxicity. We have developed and applied to isolated human cells several in vitro techniques (glucocorticoid receptor analysis, response of cells to added glucocorticoid in terms of radiolabeled isotope incorporation and decreased cell viability) which might allow prediction of antitumor response prior to initiation of glucocorticoid therapy. The primary objective of the proposed research is to study tumor glucocorticoid receptors and in vitro glucocorticoid sensitivity in adults with lymphoma to see if we can use these in vitro techniques to select patients who will benefit from glucocorticoid therapy. Secondary objectives are to determine the diagnostic and prognostic utility of these in vitro glucocorticoid analyses and to develop an increased understanding of the mechanisms of glucocorticoid sensitivity and resistance in lymphoma.

We propose to accomplish our objectives through a unique collaboration between investigators at the University of Minnesota, experienced in clinicopathologic studies in adult lymphoma, and investigators at Dartmouth Medical School, experienced in in vitro glucocorticoid studies. Lymphoma patients will undergo diagnosis, staging and treatment at Minnesota; specimens of their malignant and normal lymphoid tissue will be shipped to Dartmouth for in vitro glucocorticoid studies. Results of in vitro glucocorticoid analyses will be correlated with histology, lymphocyte surface markers, treatment status, in vivo antitumor response to glucocorticoids, response to combination chemotherapy, and survival.

This research should enable us to individualize glucocorticoid therapy in adult lymphoma so that patients likely to benefit can receive it and those unlikely to benefit can be spared significant toxicity. Many practical questions concerning large scale application of in vitro glucocorticoid analysis to lymphoma patients will be answered. A new prognostic tool for lymphoma (glucocorticoid receptors) may be defined and we may develop increased understanding of the mechanisms of glucocorticoid sensitivity and resistance.

190. COMBINATION CHEMOTHERAPY OF HODGKIN'S DISEASE (HUMAN)

Presant, C. A., Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

This is part of a broader project. A summary of this subproject is not available.

191. KARYOTYPIC ANALYSIS IN RELATION TO CANCER SUSCEPTIBILITY, ETIOLOGY AND THERAPY

Watt, J. L., Brown, T., University of Aberdeen, Cytogenetics Lab., Dept. of Genetics, *Foresterhill, Medical School Bldgs., Aberdeen AB9 2ZD, Scotland, United Kingdom*

The summary for this project is under entry no. 174.

192. SECOND CANCERS IN PATIENTS WITH HODGKIN'S DISEASE

Hutchison, G. B., Boivin, J., Hellman, S., Aisenberg, A. C., Desforges, J. F., Kim, T. H., Methot, Y., Bachand, A., Lavallee, R., Tawil, E., Thuot, C., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The summary for this project is under entry no. 172.

193. NO. 7751 - POOR RISK PATIENTS, STAGE I AND II HODGKIN'S DISEASE

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

The summary for this project is under entry no. 173.

194. CHEMOTHERAPY AND LOW DOSE RADIOTHERAPY IN HODGKIN'S DISEASE (HUMAN)

Prosnitz, L., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

The summary for this project is under entry no. 175.

195. COMBINED CHEMOTHERAPY AND RADIOTHERAPY FOR HODGKIN'S DISEASE (HUMAN)

Schnipper, L., Beth Israel Hospital, *330 Brookline Ave., Boston, Massachusetts*, 02215, United States of America

The summary for this project is under entry no. 168.

196. NO. 7552 - COMBINATION CHEMOTHERAPY AND IMMUNOTHERAPY FOR PREVIOUSLY TREATED STAGE IIIB AND IV HODGKIN'S DISEASE

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study compares two combinations of chemotherapy; one being the standard CCNU, Velban, procarbazine, prednisone combination with a non-cross-resistant combination containing bleomycin, adriamycin, vincristine and streptozotocin with alternating courses of these eight drugs in patients who have relapsed from previously treated Hodgkin's disease. We have entered no patients from this VA Medical Center. This study is part of a larger Cancer and Acute Leukemia Group B study and is still under way.

197. IMMUNOLOGICAL STUDIES AND IMMUNOTHERAPY PILOT TRIAL IN HODGKIN'S DISEASE

Grifoni, V., Tognella, S., Pierri, I., Sangiuolo, A., Scarsi, P. G., Piccardo, C., Scudeletti, M., Universita degli Studi di Genova, Cattedra Clinica Medica, *Viale Benedetto 15 2, 116132 Genoa, Italy*

OBJECTIVES: (a) To further characterize the lymphocytotoxic autoantibody present in Hodgkin's patients' serum. To identify cell subpopulations which produce it, and target cell and subcellular fractions. To study interference of levamisole with the action of such antibody. (b) To explore various modalities of intervention in order to correct the immunodeficiency of such patients, and possibly to influence the course of the fundamental disease itself.

APPROACH: (a) Lymphoid cells from peripheral blood, lymph nodes, and spleens of patients with Hodgkin's disease will be separated through Ficoll isokinetic gradient in order to identify source-cell of and target-cell for tte autoantibody. Lymphoid cell lysate and membrane will be submitted to fractionation employing disc electrophoresis and Sephadex G-200 gel filtration in order to purify the antigen(s) involved. Interference of levamisole in the in vitro reaction between the cytotoxic antibody and lymphocytes will be studied. (b) Lymphocytapheresis, autoantibody elution, and lymphocyte reinfusion should be done in subjects in which marked autocytotoxicity is present. Allogeneic lymphocyte transfusion and treatment with immunomodulator drugs should also be exploited.

PROGRESS: (a) Evidence has been produced that levamisole is capable of preventing and partially reversing the inhibition of E-rosette formation induced by Hodgkin's cytotoxic serum (Del Giacco, S., Tognella, S., Leone, A.L., Locci, F., Cornaglia, P., Sangiuolo, A., Grifoni, V.: Interference of levamisole with inhibition of E-rosette formation by Hodgkin's disease and systemic lupus eryhthematosus cytotoxic sera: Blood 53, 1002-1006, 1979).

D. PROTOCOLS

198. STREPTOZOTOCIN, BLEOMYCIN, CCNU AND ADRIAMYCIN FOR THE TREATMENT OF ADVANCED HODGKIN'S DISEASE

Kaplan, R. S., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

Because of the previously reported activity of the combination of streptozotocin 500 mg/m2 IV days 1-5, CCNU 100 mg/m2 orally day 1, adriamycin 45 mg/m2 IV day 1 and bleomycin 15 mg/m2 IM days 1 and 8 (SCAB) given at 28 day intervals in patients with previously treated Hodgkin's disease, this regimen was employed for 20 patients with stage IIIB, IVA, or IVB previously untreated Hodgkin's disease. The complete response rate in this previously untreated group was 75% (15/20). Median remission duration will be in excess of 22 months with patients still being followed from 12 plus to 48 plus months in remission. There have been 2 relapses of disease at 5 and 12 months. Toxicities seen with this regimen were similar to those seen in the previously treated group. Moderate myelosuppression was seen with platelets being affected more than white cells. Liver dysfunction occurred in 6 patients; 5 patients had weight loss presumably secondary to chemotherapy; bleomycin pulmonary toxicity was seen in 5 patients; and 4 patients has mild increases in their serum creatinines. SCAB appears to be effective therapy for patients with advanced, previously untreated Hodgkin's disease. This investigation has been terminated and replaced by a study of MOPP alone versus alternating MOPP and SCAB in advanced untreated Hodgkin's disease.

BIBLIOGRAPHIC REFERENCES: Diggs, C.H., Wiernik, P.H. and Sutherland, J.C.: Treatment of Advanced Untreated Hodgkin's Disease with SCAB - An Alternative to MOPP. Cancer (in press), 1980.

199. CLINICAL TRIAL WITH DOPP

Rahim, M. A., Islam, K. M., Khaleque, S. A., Miah, M. N., Dacca Medical College Hospital, Radiotherapy Unit, *49 E. Azimpur Govt. Estate, Dacca 5, Bangladesh*

OBJECTIVE: A new combination of four anticancer drugs, DOPP, to be used against malignant lymphoma to evaluate a) its toxicity, if any, on human subjects, and b) therapeutic effects, in comparison to MOPP.

APPROACH: DOPP will be used in cycles; patients will be randomized after histological examination of specimens.

Maximum of six cycles will be administered. Dose schedules are: Doxorubicin - 20 mg/m2, IV, D 1 and 13, Oncovin - 1.0 mg/m2, IV, D 3 and 15, procarbazine - 50-200 mg/day, PO, D 1-15, prednisolone - 40 mg/day, PO, D 1-15, q. 28 days after examination of blood. Dose to be adjusted according to nadir of leukocytes and platelets.

200. PROTOCOL FOR TREATMENT OF HODGKIN'S DISEASE IN CHILDREN

Lobo, J. F., Garcia, I., Jimenez, E., Camacho, A., Jimenez, R., Hospital Nacional de Ninos, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: 1) To evaluate children with previously untreated Hodgkin's disease, and, based on the clinical stage IA-IIIA (without laparotomy), assign them to two different therapeutic modalities: chemotherapy alone or chemotherapy plus radiotherapy. 2) To evaluate the use of radiotherapy exclusively restricted to invaded areas. 3) To determine the usefulness of cyclophosphamide, vinblastine, prednisone and procarbazine (CVPP) in 28-day cycles for a total of 6 cycles. 4) To determine the usefulness of CVPP plus adriamycin, onocovin and bleomycin (CAVOBPP) without radiotherapy in induction of remission and, then, in maintenance in children with stage IIIB and IV Hodgkin's disease.

PROGRESS: To date 11 patients have been accepted to the protocol. Six have completed treatment and have been in remission 7-18 months. Five are still under treatment.

This protocol is undertaken in coooperation with the Grupo Latinoamericano de Tratamiento de Hemopatias Malignas (GLATHEM-79). (Translated)

201. PROTOCOL FOR THE COMBINATION CHEMOTHERAPY OF DISSEMINATED HODGKIN'S DIESASE

Neiman, P., Sullivan, K. M., Einstein, A., Fred Hutchinson Cancer Research Center, Division of Oncology, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This study evaluates the benefit of the addition of non-cross-resistant combination therapy to standard MOPP chemotherapy of stage IIIB and IVB Hodgkin's disease. Four monthly cycles of MOPP are administered. Patients in a complete or excellent partial remission are randomized to receive 4 courses of either a standard adriamycin-based regimen (adriamycin, bleomycin, Velban, and DTIC) or a BCNU-based treatment (BCNU, Velban, bleomycin and hexamethylmelamine). Re-staging to demonstrate remission is performed and treatment is then discontinued. Remission induction toxicities and relapse rates are monitored. Treatment is delivered on an outpatient basis, often by practicing physicians in the community.

202. CLINICALLY CONTROLLED STUDY OF CVPP VS. CCVPP (CVPP PLUS CCNU) IN MALIGNANT LYMPHOMAS (ABBREV)

Pavlovsky, S., Morgenfeld, M. C., Grupo Argentino de Tratamiento de la Leucemia Aguda, *P. de Melo 3081, 1425 Buenos Aires, Argentina*

DESCRIPTION: This is a phase III study designed to evaluate whether CVPP (cyclophosphamide, vinblastine, prednisone and procarbazine) combination or CCVPP (CVPP plus CCNU) is more effective in inducing and prolonging complete remissions in patients with lymphomas.

Therapeutic regimen for patients with malignant lymphoma stages I and II B, III and IV A and B: INDUCTION: CVPP: Cyclophosphamide 600 mg/sq m i.v. day 1, vinblastine 6 mg/sq m i.v. day 1, procarbazine 100 mg/sq m orally days 1-14, and prednisone 40 sq m orally days 1-14. CCVPP: CVPP plus CCNU 75 mg/sq m orally day 1 of first, second, third and fifth cycle. Both schemes every 28 days x 6 months, then every 2 months x 6, every 4 months x 3 and every 6 months x 2.

MAINTENANCE: Patients continue on the same therapy as that received for induction. A course will be administered every 2 months the first year, every 4 months the second year and every 6 months the third year.

A total of 281 Hodgkin's disease (HD) and 166 non-Hodgkin's lymphoma (NHL) patients were evaluable. The rate of complete remission in HD with CVPP was 71% (112/158), and 79% (110/140) with CCVPP; in NHL - with CVPP (41/83) 49% and with CCVPP (46/83) 55%. Both differences are not significant. The duration of complete remission in HD was similar in both schedules with more than 50% of patients still in complete remission at 48 months. In NHL at 36 months 52% of the CVPP group and 41% of the CVPP group remain in complete remission.

203. OMRF 7804 - CCNU/CIS-PLATINUM COMBINATION CHEMOTHERAPY FOR REFRACTORY LYMPHOMA, PHASE II

Bottomley, R. H., Hussein, K. K., Murray, J. L., Grozea, P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

OBJECTIVES: The objective of this phase I-II study is to determine the efficacy of a two-drug combination which includes CCNU and cis-platinum in the treatment of alkylator-resistant lymphoma and to determine the toxicity of this combination.

PLAN: Prior to infusion of any drugs, a diuresis will be established by giving 25 grams of mannitol in 1 liter of D5.45 NS over 2 to 3 hours. Following this, cis-platinum at a dosage of 75 mg/m2 will be given by 24-hour infusion. The cis-platinum will be diluted in 2 liters of fluid, and additional fluid will be given to maintain urine output of at least 200 cc/hour. Preliminary unpublished results from Stanford indicate decreased toxicity of 24-hour infusions. Following the administration of the cis-platinum, CCNU will be given orally, at a dosage of 45 mg/m2. Therapy is to be repeated at 3 week intervals and dosage adjustments, based upon values obtained just before the next course of treatment.

The study remains open. There are no patients registered on this study at this time.

204. PHASE II PROTOCOL FOR THE TREATMENT OF MALIGNANT LYMPHOMAS WITH ANTI-THYMOCYTE GLOBULIN

Bunn, P. A., Fisher, R. I., Minna, J. D., Cohen, M. H., Ihde, D. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

As of March 1980, 8 patients have entered this protocol. All had advanced disease unresponsive to multiple chemotherapeutic agents. Among these 8 patients, there were 3 partial responses which lasted from one month to eight months. Two patients showed no response. Three patients died before response could be evaluated. These 3 patients all died of infectious complications primarily related to their underlying diseases previously reported to this committee. One patient experienced a development of serum sickness which caused discontinuation of the treatment. There has been considerable toxicity from this protocol including the development of infections in 3 patients. All of them died from their infections. In addition all patients developed low grade fevers, several patients developed shaking chills. The preliminary conclusions are that this form of immunotherapy does cause partial remission in patients, however it is extremely toxic. Plans are to continue the study until two other patients with advanced disease have been studied.

205. VINDESINE IN THE TREATMENT OF ADVANCED CARCINOMA OF THE LUNG, LYMPHOMA, METASTATIC MELANOMA, AND BREAST OR OTHER SOLID TUMORS

Strauss, J. F., Sheehan, R. G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology/Oncology Section, *4500 S. Lancaster Rd., Dallas, Texas*, 75216, United States of America

Since no drugs are available that can produce curative treatment or even effective palliative treatment for patients with many types of solid tumors, it is important to continue clinical testing of new anti-tumor agents.

Vindesine is a new Vinca alkaloid derivative structurally similar to Vincristine which has shown activity in solid tumors in phase I and phase II testing.

The objective of this study is to add to the phase II testing by determining a response rate and duration of response of advanced carcinoma of the lung, Hodgkin's and non-Hodgkin's lymphoma, melanoma, carcinoma of the breast, and other solid tumors to Vindesine.

Patients with non-Hodgkin's lymphoma, germ-cell tumors, or small cell carcinoma of the lung will initially be considered for treatment on currently active protocols. Such patients will be considered for this study if the protocol treatment is ineffective. Patients with Hodgkin's disease or breast carcinoma will not be considered for this protocol unless there has been progression of disease following standard combination chemotherapy. Patients having tumors for which no generally effective treatment is known may be considered for this protocol before or following treatment with other antitumor agents. The drug will be administered by IV push at weekly intervals until evidence of progression of a tumor occurs.

206. CONTINUOUS INFUSION VINDESINE - A PHASE II STUDY

Wernz, J. C., Muggia, F. M., Blum, R. H., Levin, M., Ballard, H., Hamilton, L., Dunleavy, S., Downey, A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1st Ave. at E. 24th St., New York, New York*, 10010, United States of America

The summary for this project is under entry no. 144.

III. NON-HODGKIN'S LYMPHOMAS

A. DIAGNOSIS AND PROGNOSIS

207. PROGNOSTIC FACTORS IN NON-HODGKIN'S MALIGNANT LYMPHOMAS WITH EMPHASIS ON THE FUNCTIONAL APPROACH IN CLASSIFICATION OF LYMPHOMAS

Aine, R., Alavaikko, M., Helin, H., Tampere Central Hospital, Dept. of Pathology, *36280 Pikonlinna, 33520 Tampere 52, Finland*

OBJECTIVE: Evaluation of prognostic factors in non-Hodgkin's lymphoma.

APPROACH: The project consists of two closely associated parts: a) A retrospective survival study of a defined Finnish case population of non-Hodgkin's lymphomata using the Lukes-Collins classification, Lennerts classification and, in addition, Rappaport classification. b) A prospective study: a versatile analysis of lymphoproliferative disorders by means of morphology, immunology, cytochemistry and cell kinetics.

The modern immunohistochemical techniques, the immunoperoxidase method for demonstration of intracytoplasmic immunoglobulins (large cell B-lymphomas) and muramidase ('histiocytic lymphoma'), which can be performed on paraffin embedded material, are also applied to the study of the retrospective material.

208. CLASSIFICATION OF MALIGNANT NON-HODGKIN'S LYMPHOMAS ON THE BASIS OF MULTIPLE CELL MARKER ANALYSES

Pallesen, G., Madsen, M., Aarhus Universitet, University Inst. of Pathology, *c/o Aarhus Kommunehospital, DK8000 Aarhus C, Denmark*

OBJECTIVES: The objectives are to 1) characterize neoplastic cells from human non-Hodgkin's lymphomas and malignant histiocytoses by immunological and cytochemical cell markers; 2) investigate the specificity of such markers; 3) correlate the immunological and cytochemical phenotypes with morphological classifications; and 4) investigate the significance of such phenotypes for the clinical course of these neoplasms.

APPROACH: Imprints for cytochemical stains and cell suspensions for immune marker analyses are prepared from fresh biopsy material. The Kiel-classification is used as the basic morphological classification. Most of our methods have been described in detail previously: Pallesen, G., Madsen, M., and Pedersen, B.B.: B-prolymphocytic leukaemia - a mantle zone lymphoma? Scand. J. Haematol. 22. 407-416, 1979.

PROGRESS: By September, 1980, we will have investigated a total of 61 malignant lymphomas according to the design of the project (in about 1 1/2 years).

209. PARTIAL IMMUNOCHEMICAL CHARACTERIZATION OF T23 (THE SERUM MARKER MATERIAL) IN MALIGNANT LYMPHOMA

Keen, J., Walker, L. C., Imperial Cancer Research Fund, Laboratory for Immunological Markers in Cancer, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

We have attempted to characterize T23 to improve the evaluation of this serum marker and enable the development of a quantitative assay for its detection.

Our preliminary data show that T23 has a similar mobility to immunoglobulin light chain (LC) on SDS-PAGE (M.W. approximately 23,000 daltons) while its precipitation from serum by 3.5 percent polyethylene glycol and elution from Sephacryl-200 in the range 68-150,000 daltons are more compatible with the idea that T23 may be aggregated or bound to antibody in serum. However, complexing with IgG antibody was not indicated by the failure of Staphylococcal Protein A to remove T23 from serum.

Some evidence that T23 shares similar antigenic properties with immunoglobulin LC was provided by the ability of anti-LC sera to bind to T23 eluted from SDS-PAGE slab gels. This was shown by immunodiffusion and by experiments in which radioiodinated-T23 could be recovered, by Staphylococcal Protein A absorption, from mixtures to which LC antisera had been added. Bence-Jones proteins of kappa or lambda type were used as positive controls in these experiments, and while these bound only to anti-kappa or anti-lambda, respectively, T23 from Hodgkin's and non-Hodgkin's lymphoma was bound to the same extent by both kappa and lambda antisera.

Our data suggest that we are detecting an aggregated or polymeric protein which is readily dissociable into subunits. Of interest, with respect to the reactivity of T23 with LC antisera, are recent reports indicating that a number of immature B cell neoplasms export excess nomoclonal LC (Gordon et al., Immunology, 1978, 34,397). However, as T23 has a similar incidence in Hodgkin's and non-Hodgkin's lymphoma and reacts with both anti-kappa and anti-lambda sera, it may not be a tumor-specific product.

Further characterization of T23 and an investigation of its occurrence in non-lymphoreticular malignancy and other disease states are under way.

210. STUDIES ON BIOCHEMICAL MARKERS IN HUMAN BREAST CANCER, LEUKEMIA AND LYMPHOMA

Skoog, L., Karolinska Sjukhuset, Dept. of Tumor Pathology, *S10401 Stockholm, Sweden*

The summary for this project is under entry no. 25.

211. VERIFICATION OF THE VALIDITY OF THERORETICAL MODELS, PARTICULARLY OF COHEN'S MODEL FOR THE TIME-RELATED DOSE FRACTIONATION

Cavallo, V., David, V., Guerris, R., Marini, M., Porfiri, L. M., Universita degli Studi di Roma, Istituto Radiologia, *Policlinico Umberto I, Rome, Italy*

The summary for this project is under entry no. 159.

212. RADIOISOTOPE IMAGING IN EARLY DIAGNOSIS AND MANAGEMENT OF MALIGNANT DISEASE AND TUMOR-SEEKING RADIOPHARMACEUTICALS (ABBREV)

Shanta, V., Lakshmanan, A. V., Rajalakshmi, P. K., Cancer Inst., Dept. of Radiotherapy & Physics, *Adyar, Madras 600020, Madras, India*

The summary for this project is under entry no. 158.

213. THE USE OF COMPUTED TOMOGRAPHY FOR SCREENING OF JAW LYMPHOMA

Kummoona, R. K., Ismail, M., University of Baghdad, School of Dentistry, Dept. of Oral Surgery, *Baghdad, Iraq*

OBJECTIVE: Study of the jaw lymphoma, Middle East variety, a clinical-pathological entity which differs from Burkitt's lymphoma in clinical behavior, response to treatment and possibly in its etiology. The tumor first appears in the premolar-molar region. Children suffering from jaw lymphoma die because of visceral metastasis. The use of postmortem studies in Iraq is severely restricted because of religious reasons and it is difficult to asses which organ was invaded by metastases.

CT scans might asses the extent and distribution of the tumor masses in the visceral organs by metastases, by using both coronal and transverse planes. CT scans were sufficiently characteristic to permit clinical diagnosis of most jaw lymphoma cases with visceral metastases. Research is in progress to correlate these findings with the causative agent of jaw lymphoma.

214. LYMPHOGRAPHY IN ONCOLOGIC PATIENTS

Dunnick, N. R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, Clinical Center, Dept.

of Diagnostic Radiology, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

OBJECTIVES: To evaluate the role of lymphography in comparison with other diagnostic modalities such as ultrasound and computer tomography in the staging and follow-up of patients with appropriate malignancies.

METHODS EMPLOYED: Bipedal lymphography is routinely performed on patients with a variety of malignancies, most specifically malignant lymphomas, testicular tumors, carcinoma of the prostate, carcinoma of the ovary, and Mycosis fungoides. Follow-up radiographs are performed at periodic intervals and an evaluation of the opacified retroperitoneal lymph nodes is made to assess disease progression.

MAJOR FINDINGS: Bipedal lymphograms performed on a series of 28 patients with carcinoma of the pancreas demonstrated extrapancreatic abnormalities in 4 patients. Indication of extrapancreatic disease may render these patients inoperable.

A method for delivering intralymphatic contrast material to patients who have undergone previous amputations making the usual dorsal pedal lymphatic route impossible was described.

Lymphography has been useful as one of several modalities in following patients with carcinoma of the prostate. It is limited in part by the relatively poor filling of retroperitoneal lymph nodes in older patients. Bipedal lymphography has thus far been quite useful in patients with testicular carcinoma, ovarian carcinoma, and malignant lymphomas. The better detail provided by lymphography is helpful in small sites of metastatic disease. Extranodal disease is more easily detected by computer tomography. Bulky disease can usually be readily identified by either method.

215. CORRELATION OF MORPHOLOGICAL CHARACTERISTICS OF NON-HODGKIN'S LYMPHOMAS AND LEUKEMIAS WITH SURFACE IMMUNOGLOBULIN

Sukumaran, M. S., Majhi, U., Rajalakshmi, K. R., Cancer Inst., Dept. of Pathology, *Adyar, Madras 600020, Madras, India*

The study of cellular characteristics of tumors has acquired great significance for determining the prognosis of non-Hodgkin's lymphomas and acute lymphatic leukemias. There have been many attempts to classify these tumors, based on morphological, functional, or immunological characteristics, into T and B cell lymphomas and leukemias. None of these methods appears to be specific when used singly. The clinical behavior and the prognosis of the condition depends on the cell type. We intend to study the cellular characteristics by combining morphological, cytochemical and immunological methods, and to type these into B cell and T cell lymphomas or leukemias and correlate these findings with the clinical behavior.

The study of surface immunoglobulin is done by immunofluorescence technique using FITC labelled anti-IgG and IgM antisera. The tumor cell suspension is stained by direct method.

Impression smear from lymph nodes and peripheral blood smears are used for cytochemical study of PAS and acid phosphatase stain. Morphological study is done on imprints stained by Pap smear and also on histological sections. The study has just commenced.

216. NEW IMMUNOLOGIC APPROACHES TO LYMPHOID NEOPLASMS

Frenkel, E. P., Demian, S., Forman, J., Kettman, J. R., Shay, J. W., Sheehan, R., Sheehan, W., Smith, R. G., Uhr, J. W., Vitetta, E. S., University of Texas, Health Science Center at Dallas, Southwestern Medical School, Dept. of Internal Medicine, *5323 Harry Hines Blvd., Dallas, Texas,* 75230, United States of America

These studies are directed toward the characterization of human lymphoid neoplasms, particularly those of the B cell type, in an attempt to develop a better definition of a clinically applicable taxonomy, exploit the biologic 'tumor' markers in an attempt to detect the minimal disease, and explore aspects of pathogenesis and alternative therapeutic approaches in these tumors. Antibody secreting cells making anti-tumor antibodies (anti-idiotypic antibodies) are being cloned and individual clones sought to develop a library of antisera to be used in the detection of different forms of B cell tumors in man. Exploiting the fluorescence-activated cell sorter, an 'immunologic fingerprint' of each tumor is now being carried out and a search for clinical correlates with the specific 'fingerprints' is in progress. The secreted products of these tumors and the responsiveness of tumors to mitogens and T cell signals are also being used for classification and in an attempt to apply these for the diagnosis of minimal disease. These studies propose a phenotypic characterization of the immunologic form of human lymphoid neoplasms that can be correlated with the classical histologic characterization of these tumors and provide criteria for therapeutic intervention.

BIBLIOGRAPHIC REFERENCES: Frenkel, E.P., and Kitchens, R.L. Acetyl-CoA synthetase from baker's yeast (Saccharomyces cerevisiae). Methods in Enzymology -Lipids, Part C. (ed., John Lowenstein). Academic Press, New York, 1980. Neuwelt, E.A., Maravilla, K.R., Frenkel, E.P., Barnett, P., Hill, S., and Moore, R.J. Use of enhanced computerized tomography to evaluate osmotic blood-brain barrier disruption. Neurosurg. 6:49-56, 1980.

217. EXTRA-NODAL LYMPHOMAS - IMMUNOLOGY AND ULTRASTRUCTURE

Knowles, D. M., Columbia University, College of Physicians & Surgeons, Dept. of Pathology, *630 W. 168th St., New York, New York,* 10032, United States of America

The objectives of this research proposal are: 1) To characterize immunologically and ultrastructurally the large body of neglected malignant lymphomas of extra-nodal origin, 2) to relate the results to the clinico-pathological features of these neoplasms and, in so doing, to 3) eventually be able to clearly distinguish benign from malignant lymphoreticular proliferations that commonly occur in the ocular tissues, skin, gastrointestinal tract, salivary glands and other extra-nodal sites.

Prospective immunologic analysis has shown that the extra-nodal lymphoid neoplasms are divisible into monoclonal and polyclonal proliferations. The monoclonal proliferations have been shown to be malignant by histologic criteria while the polyclonal proliferations have been shown to be benign and reactive.

Two 'by-products' of the above-described cell marker analysis of lymphoid neoplasms are 1) the observation that T lymphocyte acid alpha-naphthyl acetate esterase (ANAE) activity represents a T cell differentiation marker and 2) that the Ia antigens, preferentially expressed on normal B cells, are also useful in distinguishing neoplastic B and T cells and that both B and T cell neoplasms display phenotypic heterogeneity.

BIBLIOGRAPHIC REFERENCES: Knowles, D.M. II, Jakobiec, F.A., Halper, J.P.: Immunologic characterization of ocular adnexal lymphoid neoplasms. Amer. J. Ophthal. 87:603-619, 1979. Knowles, D.M. II, Halper, J. P., Machin, G.A., Sherman, W.: Acid alpha-naphthyl esterase activity in human neoplastic lymphoid cells: usefulness as a T cell marker. Amer. J. Pathol. 96:257-278, 1979.

218. IMMUNODIAGNOSIS OF LYMPHOMAS

Udayachander, M., Meenakshi, A., Michael, A., Muthiah, R., Cancer Inst., Dept. of Biochemistry, *Adyar, Madras 600020, Madras, India*

The summary for this project is under entry no. 161.

219. CYTOKINETIC BEHAVIOR OF NON-HODGKIN'S B-CELL LYMPHOMAS

Quaglino, D., Universita degli Studi di Modena, Istituto di Clinica Medica, *via del Pozzo, 71, 41100 Modena, Italy*

With the purpose of obtaining useful prognostic information, we have investigated the cytokinetic behavior of 19 cases of non-Hodgkin's B cell lymphomas. In all cases diagnosis was established on the basis of histological, cytoimmunological and cytochemical data. The study, carried out with the aid of autoradiographic techniques, indicates that the various histological subclasses are characterized by different metabolic and kinetic behaviors: the aggressiveness of the malignant lymphoma is closely related to the rate of growth of the lymphomatous cell populations, as assessed by the mitotic index and the labelling index with 3H-thymidine. The study of the synthesis and metabolism of RNA provides not only useful information on the energy requirements necessary for the neoplastic growth, but, when employed in association with immunohistochemical techniques for the detection of intracytoplasmic Ig synthesis, it defines more accurately the functional characteristics and the differentiation potentialities of the neoplastic populations in different cases.

220. NON-HODGKIN'S LYMPHOMA

Lennert, K., Christian Albrechts Universitat, Dept. of Pathology, *Hospitalstrasse 42, 2300 Kiel 1, Federal Republic of Germany*

OBJECTIVES: To determine clinicopathological correlations between non-Hodgkin's lymphoma; frequency of the different types; haematological and blood protein/clinical data.

B. RADIOTHERAPY

221. PHYSICAL ASPECTS OF TOTAL SKIN ELECTRON IRRADIATION

Padikal, T. N., Glatstein, E., Fraass, B. A., Roberson, P. L., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Physics & Computer Automation Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The Mev XII linear accelerator has been modified for use in total skin electron irradiation, such as mycosis fungoides. Dosimetric features have been ascertained and treatment of mycosis fungoides patients has been initiated.

222. TREATMENT OF ADVANCED NON-HODGKIN'S LYMPHOMAS OF AGGRESSIVE HISTOLOGIC TYPE IN ADULTS - STUDY NO. 2

Neiman, P., Sullivan, K. M., Groudine, M., Griffin, T., Kadin, M., Fred Hutchinson Cancer Research Center, Division of Oncology, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This project evaluates the utility of combined modality therapy in the treatment of advanced stage poorly differentiated lymphocytic and poorly differentiated mixed (lymphocytic and histiocytic) lymphomas. Surface markers are performed in addition to light microscopy of the lymphoma tissue. Induction therapy consists of 4 monthly cycles of combination chemotherapy (Cytoxan, adriamycin, vincristine, prednisone and hexamethylmelamines). Patients achieving a complete or excellent partial remission are randomized to receive: (1) Continued chemotherapy; (2) total body irradiation followed by 4 courses of CHOP; (3) fractionated hemibody irradiation followed by 4 courses of CHOP. Complete remission is demonstrated on restaging and therapy is discontinued. Treatment is delivered on an outpatient basis, often by practicing physicians in the community. The benefits of two different forms of irradiation consolidation are compared to the chemotherapy regimen. Data are periodically updated to assess the duration of remissions or development of late toxicities.

223. IRRADIATION VS CHEMOTHERAPY OF LYMPHOCYTIC LYMPHOMA (HUMAN)

Schreiber, A. D., University of Pennsylvania, School of Medicine, Dept. of Medicine, *36th & Hamilton Walk, Philadelphia, Pennsylvania*, 19174, United States of America

This is part of a broader project. A summary of this subproject is not available.

224. HISTIOCYTOSIS X (HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

C. CHEMOTHERAPY AND IMMUNOTHERAPY

225. NON-HODGKIN'S LYMPHOMA - CHEMOTHERAPY FOR STAGE III AND IV DISEASE

Lister, T. A., Bell, R., Brearley, R. L., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The studies of single agent versus combination chemotherapy for 'favorable' histological type and intensive chemotherapy with central nervous system prophylaxis and continuous maintenance therapy for 'unfavorable' histological type were closed to entry in 1977 and 1978 respectively. A total of 125 cases were entered.

Present analysis confirms the trends reported previously. 1. Both Kiel and Rappaport histopathological classifications may be used as prognostic guides, although the former may be 'biologically' more correct. 2. The bulk of tumor at presentation is the best guide to prognosis, with survival for patients with Stage III disease being significantly longer than that of those with Stage IV disease, regardless of histological type. No patient with Stage III non-Hodgkin's lymphoma of 'unfavorable' histology has relapsed after 18 months and not one has died after three years, suggesting that this is the group in which the best improvement in therapy has been seen. Stage IV non-Hodgkin's lymphoma of 'unfavorable' histology has a very poor prognosis when treated with OPAL.

226. THE USE OF INTRAVENOUS CYCLOPHOSPHAMIDE AND OTHER CYTOTOXIC DRUGS IN TREATMENT OF JAW LYMPHOMA

Kummoona, R., Al Atar, A., University of Baghdad, School of Dentistry, Dept. of Oral Surgery, *Baghdad, Iraq*

OBJECTIVE: To determine the immediate and long-term effects of intravenous cyclophosphamide and other cytotoxic drugs on a limited number of cases of jaw lymphoma. The objectives will be determined by observing the differences in response rates and duration of remission in cases at early stages or in advanced cases with visceral metastasis. We would also like to determine why a tumor which is histologically similar to Burkitt's lymphoma does not respond clinically and therapeutically in the same way.

227. CONTINUED CLINICALLY ORIENTED STUDIES ON ENDOCRINE THERAPY AND CHEMOTHERAPY OF CANCER

Nordenskjold, B., Radiumhemmet, *S10401 Stockholm, Sweden*

OBJECTIVE: The aim is to further characterize the biology of human mammary carcinoma and lymphomas and to continue our development and evaluation of predictive tests in order to improve curative and palliative treatment of these malignancies.

APPROACH: We have developed methods for measuring DNA synthesis in needle aspirates with 3H-thymidine autoradiography. This technique is used to correlate DNA synthesis with prognosis, histology and response to endocrine therapy and chemotherapy of non-Hodgkin's lymphomas and breast cancer.

We have also developed new technology for measurement of steroid hormone receptors in open biopsies and in needle aspirates from breast cancer and lymphomas. The techniques are based on isoelectric focusing in polyacrylamide gel and are applied to both estrogen and glucocorticoid receptors. The receptor data are correlated to pathology, clinical course and response to endocrine therapy and chemotherapy.

PROGRESS: The initial phase of this work has been published (Nordenskjold et al., Acta Cytologica 20, 137, 1976).

228. DISTRIBUTION AND FUNCTION OF LYMPHOID SUBPOPULATIONS IN ACUTE LYMPHOBLASTIC LEUKEMIAS AND LYMPHOMAS

Sen, L., Estevez, M. E., Finiasz, M., Diez, R., Guintoli, J., Instituto de Investigaciones Hematologicas, Depto. de Microbiologia, *Pacheco de Melo 3081, 1425 Buenos Aires, Argentina*

The summary for this project is under entry no. 84.

229. VINDESINE IN THE TREATMENT OF ADVANCED CARCINOMA OF THE LUNG, LYMPHOMA, METASTATIC MELANOMA, AND BREAST OR SOLID TUMORS

Kramer, B. S., Weiner, R. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Gainesville, Florida*, 32601, United States of America

The summary for this project is under entry no. 186.

230. CONTROL OF EMOTIONAL DISTRESS IN CANCER CHEMOTHERAPY

Leventhal, H., Love, R., Carbone, P., Nerenz, D., Ringler, K., University of Wisconsin, Madison Campus, School of Letters & Science, Dept. of Psychology, *500 Lincoln Dr., Madison, Wisconsin*, 53706, United States of America

The proposed studies investigate behavioral reactions during chemotherapy treatment for patients with breast cancer and non-Hodgkin's lymphoma. The studies will examine the time course of three classes of behavioral response to treatment: specific bodily reactions (nausea, hair loss, pain), general systemic reactions (depression, fatigue), and coping reactions (communication with staff, maintenance of social and work relationships) during the initial 6 to 12 months of chemotherapy treatment. Based on a theoretical model of stress management, we will focus on a series of factors expected to affect behavioral reactions to chemotherapy and willingness to remain in treatment. These include: (1) Symptomatic experience - number, site, and size of tumors available to touch and other sensory experience, as well as the range of symptoms produced by treatment, (2) interpretations of symptoms - perceived causes and consequences, (3) perception and use of available coping resources, and (4) criteria for evaluating coping effectiveness. Combinations of these factors can produce stable systems (patient is attending to symptoms that can be regulated by appropriate coping) or unstable systems (patient is searching for a means of controlling threatening symptoms). An unstable system can be associated with high levels of stress, inability to cope with daily events, and decisions to withdraw from therapy. Stability of the patient's response system and desire to remain in treatment should be high when tumors are palpable and responsive to treatment. A series of intervention studies is presented which aims at minimizing departures from optimal therapy induced by psychological distress. In the interventions, a set of patient preparation procedures will be devised to reduce feelings of hopelessness or loss of control over the threatening and distressing aspects of illness and treatment. The preparation process will use visual and tactile devices to create accurate expectations for treatment experiences and provide practice for coping responses.

231. GLUCOCORTICOID RECEPTORS IN ADULT MALIGNANT LYMPHOMA

Bloomfield, C. D., Smith, K. A., Munck, A., Peterson, B. A., Gajl Peczalska, K. J., Frizzera, G., McKenna, R. W., Goldman, A., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Medicine, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The summary for this project is under entry no. 189.

232. TREATMENT OF ADVANCED NON-HODGKIN'S LYMPHOMAS OF AGGRESSIVE HISTOLOGIC TYPE IN ADULTS - STUDY NO. 2

Neiman, P., Sullivan, K. M., Groudine, M., Griffin, T., Kadin, M., Fred Hutchinson Cancer Research Center, Division of Oncology, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

The summary for this project is under entry no. 222.

233. CHROMOSOME STUDIES IN PATIENTS WITH THERAPY INDUCED REMISSION OF LYMPHOMA

Garson, O. M., Cooper, I. A., Ding, J. C., Schwarz, M., University of Melbourne, St. Vincent's Hospital, Cytogenetic Unit, *Fitzroy, Victoria 3065, Australia*

The summary for this project is under entry no. 184.

234. IRRADIATION VS CHEMOTHERAPY OF LYMPHOCYTIC LYMPHOMA (HUMAN)

Schreiber, A. D., University of Pennsylvania, School of Medicine, Dept. of Medicine, *36th & Hamilton Walk, Philadelphia, Pennsylvania*, 19174, United States of America

The summary for this project is under entry no. 223.

235. CELL CONTROL IN INTEGUMENTAL CANCER

Van Scott, E. J., Urbach, F., Vonderheid, E. C., Harper, R. A., Mann, S. J., Davies, R. E., Temple University, School of Medicine, Dept. of Dermatology, *3322 Broad St., Philadelphia, Pennsylvania*, 19122, United States of America

CANCER BIOLOGY: In vitro cell kinetics and growth potential of normal keratinocytes and fibroblasts and these cell types from benign and malignant hyperplastic skin disease of hyperplasia are compared. Cellular defects in these cell types, i.e., defect in DNA synthesis, response to hormones, DNA repair, mucopolysaccharide and collagen metabolism are studied. Blood levels of polypeptide hormone, epidermal growth factor, and its role in hyperplastic cutaneous disorders are determined.

CARCINOGENESIS: Carcinogenic potential of pharmacologic agents (e.g., mechlorethamine, psoralen-ultraviolet light) is monitored in laboratory animals which have received cutaneous administration of such agents and in patients receiving such agents therapeutically.

CANCER THERAPY: Therapeutic control of the lymphoma mycosis fungoides by single agents and combinations thereof is pursued. Agents include topical and systemic drug materials as well as physical agents.

BIBLIOGRAPHIC REFERENCES: Haynes, H. A. and Van Scott, E. J.: Chapter on cutaneous lymphomas in: Dermatology in General Medicine, ed. T. B. Fitzpatrick, et al., McGraw-Hill, New York, pp. 749-767, 1979. Tam, D. W., Van Scott, E. J. and Urbach, F.: Bowen's disease and squamous cell carcinoma in a patient with psoriasis after topical, systemic and PUVA therapy. Arch. Dermatol. 115:203-204, 1979.

236. MODIFIED SLA 2-L2 THERAPY FOR NON-HODGKINS'S LYMPHOMA

Humphrey, G. B., University of Oklahoma, Health Science Center, School of Medicine, Dept. of Pediatrics, *Box 26901, Oklahoma City, Oklahoma*, 73190, United States of America

This is part of a broader project. A summary of this subproject is not available.

237. COMBINATION CHEMOTHERAPY FOR NON-HODGKIN'S LYMPHOMA (HUMAN)

Schnipper, L., Beth Israel Hospital, *330 Brookline Ave., Boston, Massachusetts*, 02215, United States of America

This is part of a broader project. A summary of this subproject is not available.

238. CHEMOTHERAPY AND IMMUNOTHERAPY OF MYCOSIS FUNGOIDES

Van Scott, E. J., Temple University, School of Medicine, Dept. of Dermatology, *3322 Broad St., Philadelphia, Pennsylvania*, 19122, United States of America

This is part of a broader project. A summary of this subproject is not available.

D. PROTOCOLS

239. NON-HODGKIN'S LYMPHOMA - INTENSIVE COMBINATION CHEMOTHERAPY FOR ADVANCED NON-HODGKIN'S LYMPHOMA OF ALL HISTOLOGICAL TYPES

Bell, R., Lister, T. A., Ford, J. M., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The following two experimental programs were investigated for patients with Stage III and IV non-Hodgkin's lymphoma of unfavorable histology and for Stage III and IV non-Hodgkin's lymphoma of favorable histology with very extensive disease at presentation (i.e., poor prognosis with favorable histology): 1. Phase II study of a high dose regime of cyclophosphamide and prednisolone with vincristine and adriamycin in Stage III and IV non-Hodgkin's lymphoma of unfavorable histology. Twenty-four consecutive untreated patients have been entered in this study since May 17, 1978. Preliminary analysis was performed in April, 1979, at which time 16 patients were available for evaluation. Only one of these patients had stage III disease; the remainder were stage IV. Three presented with SVC obstruction, six had bulky abdominal disease, three had ascites, eight had liver involvement, and two had CNS involvement at presentation. At the time of analysis, nine patients had died and the median survival of the series was 4.7 months. Eight patients had died in therapy, five of infection while neutropenic, two of gastro-intestinal bleeding and one of massive tumor lysis. One patient had died of progressive disease, remote from therapy. Seven patients were alive and in therapy; three of these were disease-free, two were responding to therapy and two were non-responders. This series is biased by adverse presentations, and the short median survival in part reflects this. The therapy is extremely toxic with eight treatment-related deaths. Detailed analysis is currently being performed. 2. Phase II study of a high dose regime of cyclophosphamide and prednisolone in advanced non-Hodgkin's lymphoma of favorable histological type. Very high doses of both cyclophosphamide (2.5-5.0 gm/sq. m) and prednisolone (1.0 mg/sq. m x 5) at approximately 21-day intervals were given to 22 patients with advanced stage IV non-Hodgkin's lymphoma of favorable histology. Transient and often dramatic reduction of disease was seen in 19 of the patients at days 7-14 after therapy; however, by days 21-28, the disease had frequently 'regrown'. Six patients achieved complete remission and six partial remission. All complete remitters had a previous disease pattern of remission. (Text Abridged.)

240. STUDY OF TWO CHEMOTHERAPY REGIMENS FOR PREVIOUSLY TREATED NON-HODGKIN'S LYMPHOMAS

Kaplan, R. S., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

Thirty-one patients with advanced previously treated non-Hodgkin's lymphomas who had failed to attain complete remission on combination chemotherapy or who had relapsed after receiving combination chemotherapy and attaining a remission have been treated with one of two combinations of drugs. Initially, patients who had not received an adriamycin-containing regimen were treated with a combination of adriamycin, VM-26 and bleomycin and patients who had received adriamycin previously were treated with platinum and VM-26 and bleomycin. Ten patients were treated with the platinum-containing combination, none of whom responded to treatment. This arm was therefore discontinued. Thereafter all patients were treated with the adriamycin combination regardless of previous exposure to the drug. Twenty-one patients have received this therapy with five patients attaining complete remissions and five patients partial remissions. Nine patients failed to respond and the remainder of the patients are still receiving treatment. Toxicities that have been seen have been predominantly myelosuppression. Because of its inactivity, the platinum arm has been discontinued while the adriamycin combination seems relatively active regardless of previous exposure to the drug and continues to accrue patients.

241. EVALUATION OF TWO MAINTENANCE PROGRAMS FOR CHILDHOOD NON-HODGKIN'S LYMPHOMA WITHOUT PREVIOUS TREATMENT (ABBREV)

Pavlovsky, S., Bonesana, A. C., Grupo Argentino de Tratamiento de la Leucemia Aguda, *P. de Melo 3081, 1425 Buenos Aires, Argentina*

OBJECTIVES: 1. Compare, with an historic control (Protocol 6-LRS-73), whether the adding of adriamycin and cyclophosphamide to vincristine and prednisone in a sequential form and the extension of vincristine administration to 8 weeks increases the percentage of complete remissions, the duration of same and the survival. 2. Evaluate whether preventive treatment of the CNS with intrathecal (IT) methotrexate alone is as effective as prevention with cobalt 60 to the cranium and IT methotrexate. 3. Continue with the two treatment groups of maintenance COPP (lymphoma type) or 6-mercaptopurine, methotrexate, cyclophosphamide (leukemia type) to evaluate their influence on duration of complete remission.

METHODS: Induction (common to all the patients): VCR 1.5 mg/sqm iv days 1, 8, 15, 21, 29, 36, 43 and 50; PRED 40 mg/sqm/day orally days 1 to 14, 22 to 35 and 52 to 61; CTX 600 mg/sqm iv days 1 and 15; ADR 45 mg/sqm iv days 1, 22 and 43. Radiotherapy 3500 rads in the more bulky lymph node areas for 4 weeks; MTX 12 mg/sqm IT days 1, 22, 36, and 43; DM 1 mg/sqm IT days 1,22, 36 and 43. Maintenance: Randomization: Arm I: Combination chemotherapy with: CTX 600 mg/sqm iv days 1 and 8; VCR 1.4 mg/sqm iv days 1 and 8; PCB 100 mg/sqm/day po for 10 days; PRED 40 mg/sqm/day po during 14 days on the first and fifth cycle. Arm II: Combination chemotherapy with: 6MP 2.5 mg/kg/day po; MTX 15 mg/sqm/week po or im; CTX 300 mg/sqm/week orally. Every 3 months reinforcement courses with: VCR 1.5 mg/sqm iv day 1; PRED 40 mg/sqm po days 1 to 7.

PROGRESS REPORT: By June 1978 25 patients had been entered to the protocol, of whom 20 were evaluable and 18 (90%) achieved complete remission. Seven (100%) out of 7 stage I and II and 11 (85%) out of 13 with stage III and IV achieved complete remission. Three out of 6 from Arm I relapsed compared to 3 out of 12 from Arm II.

242. PROTOCOL FOR THE RANDOMIZED TREATMENT OF CUTANEOUS T-CELL LYMPHOMAS AND MYCOSIS FUNGOIDES AND SEZARY SYNDROME

Bunn, P. A., Kumar, P. P., Bilek, F., Fischmann, B. A., Schechter, G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Oncology Section, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

During the past year 22 patients have been entered on this randomized study; 11 patients were randomized to the conservative arm and have received topical nitrogen mustard alone, 11 patients were randomized to the combined modality arm with combination chemotherapy and electron beam radiation. There have been no unexpected complications associated with the treatment in either arm. At this time it is much too early to reach any conclusions from this study. We plan to continue the study until approximately 100 patients have been entered on this study as we had originally intended.

243. PHASE II PROTOCOL FOR THE TREATMENT OF MALIGNANT LYMPHOMAS WITH ANTI-THYMOCYTE GLOBULIN

Bunn, P. A., Fisher, R. I., Minna, J. D., Cohen, M. H., Ihde, D. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

The summary for this project is under entry no. 204.

244. METHOTREXATE AT HIGH AND MEDIUM DOSES WITH RESCUE IN LYMPHOMA PATIENTS AND IN A NATIONAL LEUKEMIA TRIAL

Polli, E., Cortellaro, M., Periti, P., Djerassi, I., Universita degli Studi di Milano, Istituto di Clinica Medica IV, *Via F. Sforza 35, 20122 Milan, Italy*

The summary for this project is under entry no. 143.

245. CLINICAL TRIAL WITH DOPP

Rahim, M. A., Islam, K. M., Khaleque, S. A., Miah, M. N., Dacca Medical College Hospital, Radiotherapy Unit, *49 E. Azimpur Govt. Estate, Dacca 5, Bangladesh*

The summary for this project is under entry no. 199.

246. PHASE II STUDY OF ARABINOSYLADENINE-5'-PHOSPHATE (ARA-A-5'-P)

LePage, G. A., Khaliq, A., University of Alberta, Cancer Research Unit, McEachern Laboratory, *Edmonton, Alberta, Canada*

The summary for this project is under entry no. 140.

247. OMRF 7804 - CCNU/CIS-PLATINUM COMBINATION CHEMOTHERAPY FOR REFRACTORY LYMPHOMA, PHASE II

Bottomley, R. H., Hussein, K. K., Murray, J. L., Grozea, P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

The summary for this project is under entry no. 203.

248. VINDESINE IN THE TREATMENT OF ADVANCED CARCINOMA OF THE LUNG, LYMPHOMA, METASTATIC MELANOMA, AND BREAST OR OTHER SOLID TUMORS

Strauss, J. F., Sheehan, R. G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology/Oncology Section, *4500 S. Lancaster Rd., Dallas, Texas*, 75216, United States of America

The summary for this project is under entry no. 205.

249. COMBINED MULTICENTER AUSTRALIAN NON-HODGKIN'S LYMPHOMA TRIAL (PHASE III)

Matthews, J. R., Probert, J. C., Harvey, V., Smith, A., Varcoe, A. R., Buchanan, J. G., Auckland Hospital, Dept. of Haematology, *Park Rd., Auckland 1, New Zealand*

OBJECTIVES: To study the therapeutic and toxicity difference of a single versus two mitotic phase inhibitors in a combined drug regimen for the treatment of non-Hodgkin's lymphoma (poor prognosis histology). Drug combinations are: 1. Vincristine, Tenepoxide (M26), Adriamycin, Cyclophosphamide and Prednisone. 2. a) Vincristine, Adriamycin, Cyclophosphamide, Prednisone. b) Teneposide, Adriamycin, Cyclophosphamide, Prednisone.

APPROACH: Clinical trial with randomized entry and informed consent with full staging.

PROGRESS: Total of 120 patients entered from all centers (16 from Auckland).

250. CLINICALLY CONTROLLED STUDY OF CVPP VS. CCVPP (CVPP PLUS CCNU) IN MALIGNANT LYMPHOMAS (ABBREV)

Pavlovsky, S., Morgenfeld, M. C., Grupo Argentino de Tratamiento de la Leucemia Aguda, *P. de Melo 3081, 1425 Buenos Aires, Argentina*

The summary for this project is under entry no. 202.

E. OTHER AND NON-SPECIFIC THERAPY

251. EFFECT OF INTERFERON THERAPY ON NON-HODGKIN'S LYMPHOMA

Merigan, T. C., Stanford University, School of Medicine, Dept. of Medicine, *Stanford, California*, 94305, United States of America

This study will evaluate the effect of human leukocyte interferon on several stages and types of non-Hodgkin's lymphoma. The initial studies will be done on patients with advanced but objectively measurable disease who have failed other conventional therapy. Then, if results are encouraging, patients with 'good' risk and 'poor' risk types of histologically and clinical staged disease will be utilized to evaluate, on a controlled basis, the effect of short-term but intensive interferon therapy on disease status and recurrence. This will be done both by contrast with and in concert with conventional therapy. Careful observation of interferon pharmacokinetics, effect of treatment on clinical course, and possible side effects will be carried out throughout the trials.

252. EFFECT OF INTERFERON THERAPY ON B-CELL LYMPHOMAS

Merigan, T. C., Rosenberg, S. A., Stanford University, School of Medicine, Dept. of Medicine, *Stanford, California*, 94305, United States of America

This study will evaluate the effect of human leukocyte interferon on various B-cell lymphomas, in particular, non-Hodgkin's lymphoma. We plan to continue our Phase I and II studies in patients with advanced but objectively measurable disease. Patients with either nodular lymphocytic, poorly differentiated (NLPD) lymphoma or diffuse histiocytic (DHL) lymphoma will be studied, as well as selected chronic lymphocytic leukemia (CLL) patients, to determine the range and duration of interferon action. After determining the effect of prior therapy on the response and the optimum dosing pattern (minimal effective dose and duration as well as effect of splitting dosage), a randomized controlled trial will be conducted to determine if interferon can prolong life and decrease morbidity associated with these tumors. Interferon pharmacokinetics and side effects will also be carefully evaluated in each patient. In order to better quantitate response, where possible, circulating monoclonal B cells will be measured, as well as the tumor cell specific immunoglobulin product. To further study the mechanism behind any antitumor effect observed, a variety of potentially relevant immune parameters will be monitored, as well as the in vitro effect of interferon tumor cell lines established from some of these patients.

253. THERAPEUTIC STRATEGIES FOR NON-HODGKIN'S LYMPHOMAS OF WALDEYER'S RING

Ghilezan, N. I., Milea, N. I., Tamburlini, V. S., Mogut, D. I., Oncological Inst. of Cluj-Napoca, Cobalt, *Republicii Nr. 34-36, R3400 Cluj-Napoca, Romania*

OBJECTIVE: To determine the optimal therapeutic approach in the treatment of non-Hodgkin's lymphomas of Waldeyer's ring according to histology and clinical staging.

APPROACH: Patients with a histologically confirmed diagnosis of non-Hodgkin's lymphomas of Waldeyer's ring are eligible for study. The value of bone marrow biopsy and lymphography is investigated for the assessment of the extent of this particular type of presentation. Different treatments are planned for every stage and patients are stratified according to histologic subgroups and patterns and type of staging. The patients are randomized to receive either radiotherapy alone or RT plus COP (cyclophosphamide, oncovin, prednisone) or CHOP (plus adriamycin). The value of the treatment will be assessed by analysis of local failures and survival.

254. MICROCALORIMETRIC STUDIES OF METABOLISM IN LYMPHOCYTES FROM PATIENTS WITH NON-HODGKIN'S LYMPHOMA (NHL)

Monti, M., Brandt, L., Olsson, H., University Hospital of Lund, Dept. of Internal Medicine & Oncology, *E. Blocket, S22185 Lund, Sweden*

We have recently investigated the metabolic activity in lymphoma cells and blood lymphocytes of 14 NHL patients by microcalorimetric measurements. In all 7 patients who did not respond to treatment the heat production in lymphoid cells obtained from tumor masses was higher than in 7 other patients with a complete response to therapy. The distinction between the two groups of patients was clear and no overlapping was noted. Four of the 7 patients in the first group expired during the observation period. In the group of patients not responding to treatment 5 out of the 7 cases exhibited increased heat production in their peripheral blood lymphocytes. It is possible that the increased heat production in peripheral blood lymphocytes found in the patients who did not respond to treatment was due to a seeding of the peripheral blood with metabolically highly active lymphoma cells.

Our results suggest that a high metabolic activity in lymphoma cells is associated with an aggressive growth of the tumor tissue.

255. TREATMENT OF NON-HODGKIN'S LYMPHOMA (HUMAN)

Prosnitz, L. R., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

256. THERAPY OF LYMPHOSARCOMA-RETICULUM CELL SARCOMA

Lenhard, R. E., Johns Hopkins University, School of Medicine, Dept. of Medicine, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

This is part of a broader project. A summary of this subproject is not available.

257. MYCOSIS FUNGOIDES AND SEZARY SYNDROME

Safai, B., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

258. TILORONE IN MYCOSIS FUNGOIDES (HUMAN)

Blaylock, W. K., Virginia Commonwealth University, Medical College of Virginia, Dept. of Dermatology, *1200 E. Broad St., Richmond, Virginia*, 23298, United States of America

This is part of a broader project. A summary of this subproject is not available.

IV. SUPPORTIVE CARE OF LEUKEMIAS AND LYMPHOMAS

A. BONE MARROW TRANSPLANTATION OF ACUTE LEUKEMIA

259. BONE MARROW TRANSPLANTATION IN THE TREATMENT OF ACUTE MYELOID LEUKEMIA

GordonSmith, E. C., Harris, R. A., University of London, Royal Postgraduate Medical School, Dept. of Haematology, *c/o Hammersmith Hospital, Du Cane Rd., London W12 0HS, England, United Kingdom*

OBJECTIVE: To assess the value of allogeneic bone marrow transplantation in the treatment of acute myeloid leukemia.

APPROACH: The initial part of the program is to study the complications of bone marrow transplantation so that some of the more serious side effects may be anticipated and prevent-ed. At this stage virological studies together with recurrent lung and intestinal function studies are being carried out.

PROGRESS: The numbers of patients investigated since June 1978 are as yet too small to draw conclusions. Methods for measuring lung function and intestinal absorption in sterile conditions have been developed.

260. EVALUATION OF BONE MARROW TRANSPLANT PATIENTS FOR ACUTE LEUKEMIA

Barrett, A. J., Kay, H. E., Powles, R., Royal Marsden Hospital, Leukaemia Unit, *Downs Rd., Sutton SM2 5PT, Surrey, United Kingdom*

OBJECTIVE: When patients with acute leukemia in relapse are transplanted with bone marrow many die within the first few weeks after transplantation from a variety of complications related to their poor clinical state. It was therefore decided to evaluate the therapeutic role of bone marrow transplantation in treating patients with acute myeloid leukemia in remission and acute lymphoblastic leukemia in the second remission.

APPROACH: A schedule for pre- and post-bone marrow transplantation management and laboratory studies was set up. Patients received cyclophosphamide 60 mg per kilogram on two successive days and total body irradiation to 1000 rad at a dose rate of 2.5 rad per minute, followed by bone marrow transplantations from an HLA identical mixed leucocyte culture compatible sibling. After transplantation patients received either methotrexate or Cyclosporin-A as prophylaxis against graft-versus-host disease. Follow-up included regular bone marrow examinations for evidence of leukemia, bone marrow colony-forming assays and liver function tests, and skin or rectal biopsies when graft-versus-host disease was suspected.

PROGRESS: Between September 1977 and October 1978 14 patients with acute non-lymphoblastic leukemia and four patients with acute lymphoblastic leukemia were transplanted. Four patients (2 ALL, 2 AML) were transplanted in relapse. Two patients died from early complications of transplantation and two died nine and eleven months after transplantation from relapse of the original leukemia. Of the 12 patients with AML grafted in remission, three have died from graft-versus-host disease, two have relapsed (one of them is dead). Two patients with ALL were grafted in remission, one patient died from obscure causes possibly related to graft-versus-host disease, the other survives with graft-versus-host disease. While it is too early to evaluate the overall success of this procedure it seems clear that transplantation in remission is associated with a much higher early survival. This is related to the lack of major clinical problems in remission patients undergoing marrow transplantation.

261. TREATMENT OF ADULT ACUTE NON-LYMPHOCYTIC LEUKEMIA FOR PATIENTS LESS THAN 60 YEARS OF AGE

Appelbaum, F. R., Fefer, A., Buckner, C. D., Thomas, E. D., Cheever, M. A., Greenberg, P. D., University of Washington, School of Medicine, Dept. of Medicine, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The summary for this project is under entry no. 72.

262. AN EVALUATION OF THE ROLE OF ALLOGENEIC AND AUTOLOGOUS MARROW TRANSPLANTATION IN THE MANAGEMENT OF MALIGNANT DISEASES

Biggs, J. C., Ma, D., Pun, A., Johnson, L., Bashir, H., Penny, R., Vincent, P., St. Vincent's Hospital, Dept. of Haematology, *Victoria St., Darlinghurst, N.S.W. 2010, Australia*

OBJECTIVE: In this project, the role of allogeneic transplantation in the management of leukemia and lymphoma will be evaluated; furthermore, the role of autologous marrow transplantation will be evaluated in the management of acute leukemia, chronic granulocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma and certain solid tumors e.g., sarcomas, ovarian carcinoma and testicular tumors.

APPROACH: (a) An evaluation of cryopreservation methods is being undertaken. (b) Techniques for the measurement of viability following thawing of marrow cells are being established. (c) Allogeneic transplants following total body irradiation are being studied in acute adult leukemia during the first relapse. (d) Patients' remission marrow in acute leukemia and marrow in chronic granulocytic leukemia are being stored and used after thawing for autologous transplantation during subsequent therapy of acute relapses. (e) Cryopreservation of marrow in patients with sensitive solid tumors is being undertaken for subsequent autologous transplantation during chemoradiotherapy for relapse.

263. ALLOGENEIC AND AUTOLOGOUS BONE MARROW TRANSPLANTATION AS RADICAL AND SUPPORTIVE TREATMENT OF MALIGNANCIES

Torlontano, G., Iacone, A., Di Bartolomeo, P., Fioritoni, G., Muzii, G., Geraci, L., D'Antonio, D., Di Girolamo, G., Barboni, F., Tabacchi, P. L., Beltrandi, E., University of Chieti, Istituto di Ematologia, Ospedale Civile, *Via Paolini 1, 65100 Pescara, Italy*

At present the preliminary objective of this Unit is to avoid the use of marrow transplantation (MT) in refractory leukemia (results are usually disappointing) and to consider MT only for use in treating acute leukemias in remission. In the case of the latter, it seems possible to obtain a 'cure' of patients who have undergone MT. For this purpose, three approaches have been considered: 1) Experimental programs of chemotherapy in order to obtain the highest percentage of complete remissions; 2) study of a more efficient protective environment for the patients who are to undergo transplantation; 3) studies of improved methods for yield of granulocytes useful in the case of infections resistant to antibiotic therapy.

264. ADULT LEUKEMIA RESEARCH CENTER

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This program project grant supports a clinical and laboratory program for a 20-bed intensive care facility with emphasis on the treatment of hematologic disorders by marrow transplantation. Principle priority has been on treatment of patients with acute leukemia or aplastic anemia. Total body irradiation and/or high dose chemotherapy is utilized to condition the patient to accept the graft and to eliminate malignant cell populations. Supportive therapies include granulocyte and platelet transfusions, laminar air flow isolation, gut sterilization and sterile diets. Immunologic recovery is monitored with long-term follow up. Supporting laboratories provide information in the areas of pathology, virology, microbiology, hematology, cryobiology, cytogenetics and histocompatibility typing. Research areas include prevention and treatment of graft-versus-host disease, opportunistic infections, acceleration of immunologic recovery and prevention of recurrent leukemia, application of immunotherapy to antileukemic treatment, in vitro assays of hematopoiesis and problems dealing with transplantation between donor-recipient non-HLA indentical pairs. Data processing and biostatistic functions provide maximum utilization of information generated.

265. AUTOLOGOUS BONE MARROW TRANSPLANTATION AS AN ADJUNCT TO ABLATIVE CHEMOTHERAPY FOR THE TREATMENT OF ACUTE LEUKEMIA

Gorin, N. C., Duhamel, G., Najmam, A., Salmon, C., Muller, J. Y., Petit, J. C., Hopital Saint-Antoine, Dept. of Hematology, *184, rue du Faubourg Saint-Antoine, 75012 Paris, France*

Autologous bone marrow transplantation is now feasible in man and allows higher dosage of chemotherapy and/or radiotherapy for the treatment of malignant tumors, without the risk of lethal toxicity from myelosuppression.

The objectives of the present study are to harvest and store autologous marrow from patients with acute leukemia (AML, ALL, acute monoblastic leukemia, CML) as soon as the first complete remission is obtained. This bone marrow will later be used when a drug resistant relapse occurs, after ablative chemotherapy or total body irradiation.

Some other patients will also be treated immediately, while in complete remission, by the same ablative chemotherapy regimen, followed by autologous bone narrow transplantation, in an effort to increase tumor cytoreduction and prolong the duration of the remission as well as hopefully the overall survival.

Preliminary data have been published in: Blood Cells (in press), 1978; Blood (51, 257-265, 1978) Lancet (May 14, 1977, p. 1050); Nouvelle Presse Medicale (September 24, 1977, 6, no.31, 2741-2745); Eur. J. Cancer (submitted for publication, 1978).

266. FURTHER DEVELOPMENT OF CLINICAL BONE MARROW TRANSPLANTATION

Speck, B., Nissen, C., Gratwohl, A., Ruggero, D., University of Basel, Dept. of Internal Medicine, Div. of Hematology, Kantonsspital, *Petersgraben 6, 4031 Basel, Switzerland*

OBJECTIVES: a) To determine if Cyclosporin A (CyA) can prevent GvH in allogeneic bone marrow transplantation for acute leukemia and aplastic anemia. b) To determine its efficacy in the treatment of chronic GvH.

APPROACH: a) All new recipients of allogeneic grafts are placed on prophylactic CyA. Its efficacy in preventing GvH and other complications is determined. Its influence on the hemopoietic precursor compartment and immune function is studied in vitro. b) Its therapeutic efficacy is studied in patients from previous series who are suffering from severe chronic GvH.

267. BONE MARROW TRANSPLANTATION FOR PATIENTS WITH LEUKEMIA

Marmont, A. M., Bacigalupo, A. P., Van Lint, M. T., Reali, G., Avanzi, G., Bistolfi, F., Vitale, V., Universita degli Studi di Genova, Ospedale San Martino, Dept. of Hematology, *Genoa, Italy*

OBJECTIVE: Eradication of leukemia with supralethal chemo-radiotherapy followed by infusion of allogeneic or syngeneic marrow.

APPROACH: Conditioning regimen consisting of: Cyclophosphamide 120 mg/kg, intrathecal methotrexate 10 mg/kg x 2; and total body irradiation on day 1/0, 1000 rads midline, from a single Co source, 5-7 rads/minute, with lung shielding to achieve a homogeneous irradiation of 1000 rads also over the lung. Fractionated total body irradiation (TBI) of 1400 rads over two days in selected patients. Selection of patients: patients with leukemia, both acute lymphoid and non-lymphoid leukemias and chronic myelogenous leukemias. Selection of donors: HLA-identical, MLC negative siblings or identical twins. Marrow aspiration of 700-1400 ml in general anesthesia. Protective isolation for patients: laminar air flow rooms, with gut decontamination and sterile food. Preventive hyperalimentation: DW50 and Freeamine 8.5% 10/40 cc/kg starting from day 7 to prevent weight loss and possibly the patients' clinical perfomance during the first 50 days post-transplant. Preventive Bactrim therapy: under investigation. Preventive MTX therapy for GvHD versus preventive prednisolone: under investigation. Treatment of established GvHD: high dose 6-methylprednisolone (over 100 mg/kg intravenously during the first week). Prevention of interstitial pneumonia: lung shielding to 1000 rads. Treatment of established interstitial pneumonia: high dose 6-methylprednisolone as for GvHD. Monitoring of immune reconstitution post-transplant: serum Ig, B lymphocytes, T lymphocytes, T lymphocyte subsets, PWM-induced in vitro B cell differentiation.

PROGRESS: Transplants in 1979: 12, alive - 4/12 (leukemia 3/9, aplasia 1/3); complications for donors - none; relapse - 3/6 evaluable patients; alive in unmaintained remission - 1/9; GvHD in 6/6 evaluable patients; dead with GvHD - 0/6; interstitial pneumonia - 1/9; dead with int. pneumonia - none.

268. BONE MARROW TRANSPLANTATION IN CHILDREN WITH LEUKEMIA

Dooren, L. J., Vossen, J. M., Rothbarth, P. H., deKoning, J., Kamphuis, R. P., Academisch Ziekenhuis Leyden, Dept. of Pediatrics, *Rijnsburgerweg 10, 2333 AA Leyden, Netherlands*

The summary for this project is under entry no. 44.

269. FACTORS AFFECTING LEUKEMIC TRANSFORMATION IN VIVO

Boggs, S. S., University of Pittsburgh, School of Medicine, Dept. of Radiology/Medicine, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

The summary for this project is under entry no. 114.

270. HUMAN LEUKEMIA MARROW

Fay, J. W., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina*, 27710, United States of America

The mechanism of bone marrow failure in acute leukemia is addressed in this research project. Using short-term tissue culture techniques, bone marrow cells from normal individuals or patients with acute leukemia in remission respond in a characteristic dose-response fashion to increasing concentrations of bone marrow colony stimulating factor. Patients with acute leukemia at presentation or relapse (even early relapse) have marrow cells which have colony stimulating factor dose response curves which are blunted compared to normals. Some type of inhibition of normal marrow cell proliferation is, thus, suggested by the presence of leukemia cell clones. This work is designed to identify and characterize this inhibition using an in vitro assay of bone marrow cell growth. An assay of residual leukemia cells in marrow aliquots derived from these studies has been developed and has obvious importance in the management of patients with acute leukemia.

BIBLIOGRAPHIC REFERENCES: Fay, Joseph W., et al.: Leukopheresis Therapy of Leukemia Reticuloendotheliosis (Hairy Cell Leukemia), Blood 54: 747-749, 1979. Hanker, J.S., Ambrose, W.W., Fay, J.W., et al.: Facilitated Light Microscopic Cytochemical Diagnosis of Acute Myelogeneous Leukemia, Cancer Research 39: 1635-1639, 1979.

271. ALLOGENEIC MARROW GRAFTING FOR TREATMENT OF ACUTE LEUKEMIA

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

272. BONE MARROW GRAFTING IN ACUTE LEUKEMIA

Starling, K. A., Baylor College of Medicine, School of Medicine, Dept. of Pediatrics, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

This is part of a broader project. A summary of this subproject is not available.

B. BONE MARROW TRANSPLANTATION OF CHRONIC LEUKEMIA, UNSPECIFIED LEUKEMIA, AND LYMPHOMAS

273. APPLICATION OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN TREATMENT OF PATIENTS WITH MALIGNANT TUMORS AND CML

Bucher, U., Beck, E. A., Odavic, R., Inselspital, Dept. of Hematology, *CH3010 Bern, Switzerland*

OBJECTIVE: The objective of the research project is the evaluation of the adjuvant therapy involving transplantation of autologous bone marrow in treatment of patients with solid tumors or CML in acute blastic transformation.

APPROACH: Hemopoietic stem cells are collected from patients with solid tumors without involvement of the bone marrow, separated from the bulk of mature cells by density gradient centrifugation and cryopreserved. After intensive chemotherapy and radiotherapy the aplastic patient is rescued by reinfusion of autologous marrow and cell support. In a group of patients with CML, stem cells from bone marrow and peripheral blood collected by aspiration or by an Aminco cell separator, respectively, are splenectomized. In the blastic transformation phase intensive chemotherapy and radiotherapy will be applied with reinfusion of stored stem cells with the aim of reverting patient's disease into the chronic phase.

PROGRESS: During four years the process of cell separation and cryopreservation was tested on more than 100 normal bone marrows. A standardization of the CFU-c assay was attempted by the use of cryopreserved stimulating and target cells. This assay was used for the evaluation of the proliferation potential of frozen stem cells. A mixture of Dextran and DMSO was found to be equivalent to DMSO alone in cryoprotection of human CFU-c.

274. AUTOLOGOUS BONE MARROW GRAFTING IN PATIENTS SUBMITTED TO RADIATION THERAPY - TOTAL BODY IRRADIATION AND PATHOLOGIC STUDIES (ABBREV)

Falcetti, E., Loasses, A., Mandelli, F., Meloni, G., Universita degli Studi di Roma, Istituto Radiologia, *Policlinico Umberto I, Rome, Italy*

Cryopreserved autologous bone marrow infusions were performed on 6 patients affected by acute or chronic myeloid leukemia at the Hematology Department, University of Rome, by F. Mandelli and co-workers. Results are not reported here.

TBI with 4 MeV or 6 MeV Linac X-rays was carried out on 38 patients. (1) Fifteen patients affected by stage III or IV non-Hodgkin's lymphoma. Dosage schedule: 10 rads per fraction; 2 fr. per week; mid-plane total dose 50-240 rads. (2) Fourteen cases of ALL, after the second relapse following chemotherapy. Dosage schedule: 10 to 30 rads per fraction; 2 fr. per week; total mid-plane dose 150-225 rads. (3) Nine patients affected by ANLL, after first C.R. following chemotherapy. Dosage schedule of short-term TBI: 12.5 rads per fraction; 2 fr. per day separated by a 12-hour interval, for 5 consecutive days; total mid-plane dose 125 rads. Clinical results are under evaluation. Preliminary data on the tolerance: nadir values of platelets reached at 4-7 weeks in the major part of cases. Thrombocytopenia varied from 80,000 to 10,000 cells/microliter. Critical values appear to be unrelated to initial pre-irradiation counts, and are mainly dependent on single fraction dose. Granulocyte and lymphocyte counts oscillate widely; the reliability of cyclical models of various types of blood cell concentration is under consideration. ST-TBI was well tolerated. This last method appears to be a useful tool for studies on the association of radiation therapy and chemotherapy.

In a group of 18 patients affected by non-Hodgkin's lymphoma, cells of bone marrow and of peripheral blood were cultured as described by Pike and Robinson (1970). The appearance of colonies and clusters was recorded. Sixteen out of eighteen cases gave positive cultures. No definite results appeared related to clinical data. Effects of substitution of different types of feeder layers on colony formation from cell suspension of bone marrow were successively examined. Studies on cultures of lymphoma stem cells are in progress.

275. AUTOLOGOUS MARROW TRANSPLANTATION

Buckner, C. D., Thomas, E. D., Stewart, P., Bensinger, W., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

We propose to evaluate the effectiveness of high dose chemoradiotherapy in a variety of malignant diseases including acute leukemia, chronic granulocytic leukemia, oat cell carcinoma, malignant lymphoma, ovarian carcinoma, breast carcinoma and resistant pediatric solid tumors. Patients will have marrow cryopreserved prior to therapy and reinfused following intensive therapy with regimens developed in the syngeneic and allogeneic transplant programs. The effectiveness of this approach in terms of marrow repopulation and therapeutic effectiveness will be evaluated.

276. AN EVALUATION OF THE ROLE OF ALLOGENEIC AND AUTOLOGOUS MARROW TRANSPLANTATION IN THE MANAGEMENT OF MALIGNANT DISEASES

Biggs, J. C., Ma, D., Pun, A., Johnson, L., Bashir, H., Penny, R., Vincent, P., St. Vincent's Hospital, Dept. of Haematology, *Victoria St., Darlinghurst, N.S.W. 2010, Australia*

The summary for this project is under entry no. 262.

277. BONE MARROW TRANSPLANTATION FOR PATIENTS WITH LEUKEMIA

Marmont, A. M., Bacigalupo, A. P., Van Lint, M. T., Reali, G., Avanzi, G., Bistolfi, F., Vitale, V., Universita degli Studi di Genova, Ospedale San Martino, Dept. of Hematology, *Genoa, Italy*

The summary for this project is under entry no. 267.

278. AUTOLOGOUS MARROW INFUSION IN CHRONIC GRANULOCYTIC LEUKEMIA (HUMAN)

Kurnick, J. E., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Medicine, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

This is part of a broader project. A summary of this subproject is not available.

279. ALLOGENIC MARROW GRAFTING FOR TREATMENT OF CHRONIC MYELOGENOUS LEUKEMIA (HUMAN)

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

280. SURVIVAL MODELS WITH GENETIC PARAMETERS

Holt, J. D., University of Guelph, Dept. of Mathematics & Statistics, *Guelph, Ontario*, N1G 2W1, Canada

It is proposed to develop statistical models for the study of the major histocompatibility complex (MHC). Models and analyses which allow one to take the immunogenetic system into account when relating patients' survival times to various treatment and prognostic factors will be developed. These models can then be used to study the effects of the MHC on the survival of leukemia patients who have received marrow transplants. Deaths due to other causes will be taken into account.

Statistical models and analyses will be further developed for matched-pair retrospective studies when a (possible causal) study factor is quantitative. More generally, models with both multivariate responses (study factor) and multivariate confounding variables will be developed for retrospective studies. Robustness of the models to the sampling scheme and measurement error will be investigated.

Genetic parameters will be incorporated into survival time models in order to allow for the inclusion of relatives at various distances from the proband in familial studies. Censored time-data and competing causes of death will be taken into account. Such models can be used to investigate the relationships between genotype, environment, and specific types of cancer.

Binary-response regression models and proportional hazard models incorporating genetic parameters are being developed. Empirical studies are being made of Breslow and Powers (1978) work on retrospective studies and of the appropriateness of discriminant analysis (Fisher's) as an approximate analysis.

281. REMOVAL OF RESIDUAL LEUKEMIC CELLS FROM REMISSION BONE MARROW PRIOR TO AUTOLOGOUS TRANSPLANTATION

Hoffbrand, A. V., Janossy, G., Prentice, H. G., University of London, Dept. of Haematology, c/o The Royal Free Hospital, *Pond Street, London NW3 2QG, England, United Kingdom*

OBJECTIVE: To determine whether it is feasible to treat selected patients with leukemia by autologous bone marrow transplantation after removal of leukemic cells in vitro.

APPROACH: Purified antibodies to antigens on leukemic or lymphoma cells, e.g., thymocyte antigens or light chain of immunoglobulins, will be prepared and used to remove malignant cells in vitro from bone marrow of patients with these diseases. After total body irradiation or cytotoxic therapy, the marrow will be used to rescue the patients.

PROGRESS: Initial studies of bone marrow freezing and preparation of purified antisera are under way.

282. MARROW GRAFTING IN TREATMENT OF HEMATOLOGIC MALIGNANCIES

Storb, R. F., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

Over the past years the Division of Oncology at the University of Washington has been involved in a continuing program of marrow transplantation for the treatment of patients with advanced, otherwise fatal malignant and non-malignant hemopoietic diseases. A number of grafted patients have become long-term survivors without recurrence of their original disease and without occurrence of graft-versus-host disease. Many patients, however, have died from recurrent disease or, more frequently, from complications related to the transplant. Further improvement in clinical marrow grafting hinges upon progress in and better understanding of at least three major areas of study: 1) Recovery of immunologic reactivity in marrow graft recipients, 2) understanding of mechanisms of stable graft-host tolerance and of graft-versus-host disease, 3) methods of recognizing and overcoming sensitization of a marrow graft recipient by previous blood transfusions. It is the objective of this proposal to conduct an immunologic investigation into those three areas of study.

BIBLIOGRAPHIC REFERENCES: Atkinson, K., Meyers, J.D., Storb, R., Prentice, R.L. and Thomas, E.D.: Varicella-zoster virus infection after marrow transplantation for aplastic anemia or leukemia. Transplantation 29: 47-50, 1980. Ringden, O., Witherspoon, R.P., Storb, R., Ekelund, E. and

Thomas, E.D.: Increased in vitro B-cell IgG secretion during acute graft-versus-host disease and infection. Observations in 50 human marrow transplant recipients. Blood 55: 179-186, 1980.

283. AUTOLOGOUS BONE MARROW RESCUE IN LYMPHOMA AND NEUROBLASTOMA

Ekert, H., Ellis, W. M., Waters, K. D., Royal Children's Hospital, Dept. of Clinical Haematology & Oncology, *Flemington Rd., Parkville, Victoria 3052, Australia*

OBJECTIVE: To determine whether autologous marrow rescue can be used in the treatment of Stage III and IV malignant lymphomas and neuroblastoma.

PROJECT: Intensive chemotherapy will be used to produce remission and bone marrow will be cryopreserved when remission has been induced. Where bone marrow is free of tumor, it will be harvested prior to commencing chemotherapy. Autologous bone marrow rescue will commence 36 hours after intensive chemotherapy has been administered.

PRESENT STATUS: Project at initiation.

C. PLASMAPHERESIS, LEUKAPHERESIS, AND TRANSFUSIONS

284. STUDY OF IMMUNE COMPLEXES IN PATIENTS WITH LEUKEMIA

Hollan, S. R., Fust, G., Mod, A., National Inst. of Hematology & Blood Transfusion, Dept. of Immunochemistry, *Daroczi Ut. 24, P.O.B. 44, H1502 Budapest, Hungary*

OBJECTIVE: Study of the correlation between the concentration of circulating immune complexes (IC's) and the course of the disease in patients with leukemia. Isolation of the circulating IC's from the sera of patients, characterization of the antigen and antibody components of the complexes. Study of the IC's deposited on the surface of bone marrow and peripheral blood lymphoid cells of patients and clarification of whether the antigen and antibody components of the circulating and deposited IC's are the same.

APPROACH: Measurement of the level of circulating IC's in sera of patients with different types of leukemia by different tests (C1q binding test, C1q solubility test, complement consumption test) in parallel, in several serum samples of the same patients obtained in different stages - blastosis, remission, infectious and bleeding complications of the disease. Investigation of the effect of chemotherapy and plasmaphoresis on the IC level. Isolation of the IC's from the patients' sera by polyethylene glycol precipitation and/or adsorption chromatography on C1q-Sepharose 4B column. Separation of the antigen and antibody components of the IC's by treatment with buffer of low pH and gel filtration. Study of the ability of the separated antibody fractions to bind onto leukemic blast cells and normal peripheral blood lymphocytes. Measurement by immunodiffusion and/or passive haemagglutination of the capacity of these fractions to react with some postulated antigen part of the circulating IC's (viral antigens, leukemia-associated antigens) or the ability of the separated antigen fractions to react with antisera raised against these antigens. Study of the IC's deposited on the surface of bone marrow and peripheral blood cells of the patients by immunofluorescence, using FITC-labeled anti-Ig and anti-C3 sera as well as (after characterization of the antigen component of the circulating IC's) antisera raised against this (or these) antigen(s).

PROGRESS: Clarification of the possible role of IC's as blocking factors for the cell-mediated immune response against leukemia-associated neoantigens. Evaluation of the effect of plasmaphoresis as a possible approach for the therapy of leukemic patients. Prognostic value of the detection of circulating IC's in leukemia.

285. STUDIES OF DELAYED HYPERSENSITIVITY IN PATIENTS WITH HODGKIN'S DISEASE (HD), USING HOMOLOGOUS PLASMA

Rodriguez Lopez, E., Gonzalez, E., Ministerio de Salud Publica, Instituto Nacional de Oncologia y Radiobiologia, *Calle 29 y E Vedado, Havana 4, Cuba*

OBJECTIVE: To attempt to demonstrate that during the oncolysis produced by treatment with cytotoxics, antigenic substances pass into the patient's blood, and that these substances are capable of producing a delayed hypersensitivity reaction in another patient with HD. Plasma obtained during post-chemotherapy oncolysis will be utilized in this experiment.

METHOD: From patients with HD stages IIIA, IIIB, IIIE, IIIS, IIIES or IV, who have received a massive dose of cyclophosphamide (60 mg x kg body weight) 150 cc blood is taken at the moment of greatest clinical reduction of adenopathies and greatest increase in uric acid in the blood. The blood is conserved in heparin and the plasma which will be used for the study is separated. The intradermic test is performed using 1/10 milliliter of the plasma in patients with active HD, in remission for less than two years and in remission for over two years, patients with non-Hodgkin's lymphoma, active or in remission, and patients with active lung cancer and in remission as the control group. Interpretation of the test is similar to that of the Mantoux test.

286. SEPARATION AND COLLECTION OF LEUKOCYTES

Bottomley, R. H., Hussein, K. K., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

The objective of this study is to collect granulocytes from normal donors for the purpose of transfusion to patients with seriously compromised bone marrow in order to prevent or eradicate infection and to leukapherese patients with various types of leukemia as a form of therapy and to freeze and store leukemic cells for in vitro experimental studies.

A total of 8 V.A. patients have been registered on this protocol during this year. A total of 41 white blood cell transfusions have been given to the 8 patients. The project is ongoing with no changes in the protocol.

287. LEUKEMIA THERAPY AND NEUTROPHIL DYSFUNCTION

Craddock, P. R., Dalmasso, A. P., White, J. C., Brigham, K. L., Moldow, C. F., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Medicine, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

During the next four years, I plan to continue my studies of the interactions between circulating granulocytes, the plasma complement system and the vascular endothecium. Based on our initial studies of the acute granulocytopenia of hemodialysis and nylon fiber filtration leukapheresis, we have shown that, in both man and animals, intravascular complement activation (and the concomitant generation of C5a des arg) leads to augmented granulocyte adhesiveness and auto-aggregation. Peripheral granulocytopenia results from embolization of these aggregates to the capillary bed and their temporary sequestration therein, and the stimulated granulocytes produce local endothelial damage manifest initially by the development of interstitial edema and later by end organ dysfunction. My plan is to explore the multiple ramifications of this novel, and likely very important, chain of biological events (in vitro, in animals, and in patients). Briefly, I plan to define (1) the cellular mechanisms whereby C5a des arg induces granulocyte adhesiveness and auto-aggregation, and (2) how the stimulated cells induce disruption of endothelial monolayers. I hope to define the clinical relevance of this granulocyte sequestration as a mechanism for (3) the otherwise-unexplained granulocytopenia and (4) the vasculitis associated with disseminated intravascular complement activation (bacterial sepsis, major trauma, severe burns, endotoxinemia, pancreatitis and myocardial infarction). I plan to develop (5) our method of granulocyte aggregometry as a technique for evaluating granulocyte plasma membrane function and as an assay system for the detection of circulating C5a des arg in patients with intravascular complement activation. As is hopefully evident from our published data, the majority of the studies I propose can and will be performed in my laboratory, but, in addition, I have been sufficiently fortunate to enlist the support of three important collaborators (all of whom have worked with me in the past) - Dr. White will provide expert ultrastructural data, Dr. Dalmasso will help with advanced complement biochemistry, and Dr. Brigham will provide his sheep model which is so eminently suitable for the study of endothelial damage and end organ dysfunction in vivo. (Text Abridged.)

BIBLIOGRAPHIC REFERENCES: O'Flaherty, J.T., Craddock, P.R., Jacob, H.S. Effect of intravascular complement activation on granulocyte adhesiveness and distribution. Blood

51:720-731, 1978. Sacks, T., Moldow, C.F., Craddock, P.R., et al. Oxygen radicals mediate endothelial cell damage by complement-stimulated granulocytes - an in vitro model of immune vascular damage. J. Clin. Invest. 61:1161-1167, 1978.

288. AML IN ADULTS - THE INCIDENCE OF ALLOIMMUNIZATION TO GRANULOCYTES AND PLATELETS FOLLOWING PROPHYLACTIC TRANSFUSIONS (ABBREV)

Ford, J. M., Cullen, M. H., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Twenty-six acute myelogenous leukaemia (AML) patients received a total of 214 combined transfusions of granulocytes and platelets obtained from normal donors during a trial of prophylaxis against infection. The patients were monitored carefully for the development of transfusion reactions and whenever possible blood samples were taken to calculate the percent recovery in the circulation of granulocytes and platelets at one hour and of platelets at 20 hours. Of the 23 evaluable patients, 12 developed severe transfusion reactions to at least one donor. Transfusion reactions were accompanied by significant reductions in the recoveries of platelets and granulocytes. There was a highly significant reduction in the recoveries of granulocytes and platelets with increasing numbers of transfusions given. The results suggest that granulocyte recoveries of less than five percent at one hour and platelet recoveries of less than 15 percent at one hour or ten percent at 20 hours are indicative of alloimmunization to these cells.

Although five patients were apparently only alloimmunized to platelets, the 12 patients who had transfusion reactions and were alloimmunized to granulocytes also had low platelet recoveries. Only six patients had no transfusion reactions and were apparently alloimmunized to neither cell type. These results indicate an alarming incidence of alloimmunization following granulocyte transfusions.

289. SEPARATION OF BLOOD BY CONTINUOUS CENTRIFUGE

Thomas, E. D., Buckner, C. D., Clift, R. A., Weiden, P., Fred Hutchinson Cancer Research Center, Dept. of Medicine, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

This project is concerned with the continuous flow manipulation of cellular and humoral blood components.

Methods of improving granulocyte collection from normal donors using shunts and centrifugation will be investigated.

A prospectively randomized controlled study will evaluate prophylactic granulocytes for patients over 50 years of age receiving initial remission induction for acute leukemia.

A prospectively randomized study will compare the effect of the decision to protect patients undergoing allogeneic marrow transplantation with laminar air flow isolation or prophylactic granulocyte transfusions.

The effects of plasma exchange and continuous flow plasma immunoperfusion on immune disease and malignancy will be studied in dogs and man.

290. CELL TRANSFUSION THERAPY

Schiffer, C. A., Aisner, J., Wiernik, P. H., Terasaki, P., Kotelba Witkoska, B., Dutcher, J. P., Johnson, G., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland,* 21201, United States of America

Management of alloimmunized patients has been facilitated by further expansion of the HLA matched donor pool and continued growth of the program of autologous frozen platelet transfusion. Studies of patients with non-lymphocytic leukemia have demostrated that the development of alloimmunization is not related to the number of platelet transfusions received. With few exceptions, patients who did not develop lymphocytotoxic antibody within 6-8 weeks of platelet transfusion never developed antibody despite subsequent transfusions, possibly suggesting a state of immune tolerance to histocompatibility antigens. A randomized study comparing the rate of alloimmunization in patients receiving lymphocyte depleted and 'standard' platelet concentrations is in progress. Platelet cryopreservation using glycerol-glucose as the cryoprotective agents has demonstrated good freeze-thaw recovery but significant loss of ATP and morphologic integrity. Indium labeled granulocytes migrate to infected sites within 30 min. of transfusion and have been shown to be a relatively simple and reliable label permitting excellent scanning and kinetic analysis. Studies are in progress using this technique to determine the effect of alloimmunization on granulocyte migration after transfusion.

BIBLIOGRAPHIC REFERENCES: Schiffer, C.A., Alisner, J.: Rational approach to granulocyte transfusion therapy. In Contemporary Hematology/Oncology, LoBue, J., Gordon, A.S., Silber, R., Plenum Publishing Corp, N.Y. pp. 201-218, 1980. Love, L.J., Schimpff, S.C., Schiffer, C.A., Wiernik, P.H.: Improved prognosis for granulocytopenic patients with gram-negative bacteremia. Amer. J. Med. 68: 643-648, 1980.

291. RANDOMIZED STUDY OF HYPERTRANSFUSION IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

Ekert, H., Smith, P. J., Toogood, I., Royal Children's Hospital, Clinical Haematology & Oncology, *Flemington Rd., Parkville, Victoria 3052, Australia*

OBJECTIVES: To determine whether moderate hypertransfusion (Hemoglobin 14-18gm%) can reduce duration of neutropenia and severity of infections in ALL and to study the mechanisms of this protective effect.

APPROACH: Paired randomization has been adopted. All children receive identical chemotherapy. Blood investigations are performed 2 times a week; bone marrow culture in soft agar performed on Day 14; erythropoietin levels to be assayed in both groups of patients.

PROGRESS: Preliminary findings (Lancet I, 776, 1976) show that there was a significantly greater polymorphonuclear count on Day 10 in hypertransfusion group; significantly diminished incidence of infections; and significant reduction in interruptions to chemotherapy. Randomization of 12 pairs of children with ALL confirms these findings. Bone marrow culture has not yet been performed in sufficient numbers of patients to permit evaluation.

Randomized study (Lancet) shows significantly greater polymorphonuclear counts on Days 7 and 10 in hypertransfused group; reduction in incidence of infection and interruptions to chemotherapy. Bone marrow studies suggest that 'stem cell competition' may be the mechanism of action.

292. SUPPORTIVE CARE OF LEUKEMIC PATIENTS IN SAITAMA CANCER CENTER USING CELLTRIFUGE AND HEMONETICS

Sampi, K., Sakurai, M., Tsuchimochi, T., Kaneko, A., Saitama Cancer Center, Hematology Laboratory, *818 Komoro, Ina-Machi, Kitaadachi-Gun, Saitama-Ken 362, Japan*

OBJECTIVE: It is necessary to provide support for the patients with neutropenia or infection and thrombocytopenia or bleeding of acute leukemia, especially while undergoing induction therapy. For this reason, attempts to procure granulocytes and platelets from normal donors using Celltrifuge and Hemonetics were made.

APPROACH: The equipment was an Aminco Celltrifuge from American Instrument Co., used since December of 1975, and Hemonetics Model 30, used since November 1976. Donors were not routinely screened for HL-A compatibility, but blood relatives of the patients, when available, were given first preference. Two donors were given 200 mg of hydrocortisone intravenously to increase granulocyte yield.

PROGRESS: Eighteen continuous flow centrifugations were attempted without problems. The mean number of leukocytes collected was 5.7 times 10 to the ninth power with a granulocyte differential of 45%, which was a 14.2% collection efficiency of total number of WBC passed through the centrifuge. In the hydrocortisone group the total yield of granulocytes was increased to 3.3 times 10 to the ninth power and the percentage of granulocytes collected rose to 57%.

Five procedures using Hemonetics were carried out without any problems. Eight cycles using the 225 ml. bowl size were adopted in all cases. The average yields in total platelets and leukocytes were 1.42 times 10 to the eleventh power and 2.92 times 10 to the ninth power, respectively. The majority of leukocytes were composed of lymphocytes (88%). Collection-efficiency for total platelets passed through Hemonetics was 35.2%. Maximum rise of post-transfusion platelet count was

90,000-100,000 per cubic millimeter, except for one patient who had DIC and was in the terminal stage of cancer of the stomach.

V. COOPERATIVE GROUPS

A. CANCER AND LEUKEMIA GROUP B (CALGB)

293. CANCER AND LEUKEMIA GROUP B CHEMOTHERAPY PROTOCOLS

James, G. W., Virginia Commonwealth University, Medical College of Virginia, Dept. of Medicine, *1200 E. Broad St., Richmond, Virginia*, 23298, United States of America

Patients of all ages with hemolytic malignancies and patients with various solid tumors are treated on defined chemotherapy protocols. The treatment programs are developed through group efforts and are approved both by the National Cancer Institute and by the individual institutional committees on the conduct of clinical research. The results of each study are coordinated by a designated study chairman who reports to the entire Cancer and Leukemia Group B membership three times a year. Successive treatment plans for a disease state are built on the best results obtained from one study to the next. Individual investigators design pilot studies of new chemotherapeutic drugs and if the results seem promising, the treatment is developed into a groupwide protocol.

Adjuvant treatment programs using radiotherapy and surgery are developed in a similar manner.

294. CALGB PROTOCOL 7451 - STAGE III HODGKIN'S DISEASE

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study is designed to determine if combination induction chemotherapy followed by single agent maintenance produces different frequencies of response and durations of remission and survival compared to total nodal radiation alone, total nodal radiation followed by chemotherapy or chemotherapy followed by total nodal radiation. No patients have been entered from the VA. This is part of a larger study and there are no results available at this time.

295. CALGB PROTOCOL 7612 - ACUTE LYMPHOCYTIC LEUKEMIA OF ADULTS

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study compares vincristine, predisone and L-asparaginase with and without daunorubicin for induction of remission in adults with acute lymphocytic leukemia. All patients receive CNS prophylaxis with radiotherapy and intrathecal methotrexate and maintenance with 6-MP and methotrexate. This study is designed to determine whether the addition of daunorubinicin adds to the frequency of complete remission. We have entered no patients from the Buffalo VAMC. This is part of a larger study and the results are not available.

296. COOPERATIVE STUDY - CANCER AND ACUTE LEUKEMIA GROUP B

Carey, R. W., Massachusetts General Hospital, Medical Service, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

Cancer investigators at the Mass. General Hospital and affiliated hospitals will collaborate in carrying on clinical research studies organized by the Cancer and Acute Leukemia Group B. Staff members serve in important positions in a national organization and participate in protocol design. A local protocol management office is maintained at the Cox Cancer Management Center where case acquisition is appropriately recorded and information is transmitted to the central statistical office in Scarsdale, New York. Periodic data review is carried out and updated flow sheets are reviewed and transmitted to the central office. Responsible protocol managers initiate reporting of conclusions in the medical literature. Clinical investigators attend bi-annual national CALGB meetings; monthly local meetings and special protocal writing sessions as needed.

The data coordinator and local office manager arranges human studies review with physicians, makes changes in consent forms for local use and ascertains that investigational drug supplies are adequate.

BIBLIOGRAPHIC REFERENCES: Wood, W. C., Cosimi, A.B., Carey, R. W., and Kaufman, S. D.: Randomized trial of adjuvant therapy for 'high risk' primary malignant melanoma. Surgery E3: 677-681, 1978. Rosner, F. and Carey, R. W.: Breast cancer and acute leukemia: report of 18 cases and review of the literature. Am. J. Hematology 4: 151-172, 1978.

297. SUPPORT OF CANCER AND LEUKEMIA GROUP B STUDIES, WRAMC

Blom, J., Ruymann, F., Imonen, R., Karcher, D., Neglia, W., Hirata, R. M., Kimball, D. B., Berenberg, J. L., Scialla, S., U.S. Dept. of Defense, Army, Medical Research & Development Command, Oncology Section, *Washington, District of Columbia*, 20310, United States of America

This research project consists of the Walter Reed Army Medical Center (WRAMC) contribution to all active Cancer and Leukemia Group B (CALGB) protocols for the study of experimental and standard drugs, singly and in combinations, with/without radiation therapy and immunotherapy, in patients with various neoplastic diseases. All eligible patients (adult and pediatric) with leukemias, lymphomas and other malignancies will be entered on active CALGB protocols. Follow-up, survival data, or any other information requested by the CALGB Operations Office concerning patients who are or were at one time on CALGB protocols will be provided.

298. CANCER AND LEUKEMIA GROUP B - MEDICAL ONCOLOGY SUPPORT

Kennedy, B. J., Theologides, A., Bloomfield, C. D., Kiang, D., Vosika, G., Peterson, B., Frenning, D., Hrushesky, W., Hurd, D., Kostraba, N., Vogelzang, N., Shipman, G., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Medicine, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The Minnesota Oncology Group of the University of Minnesota Medical School is a participating member of the Cancer and Leukemia Cooperative Group B for the study of hematologic neoplasms and malignant solid tumors. The Minnesota Oncology group joined the CALGB in August of 1973.

Currently, the Minnesota Oncology Group consists of a Therapeutic Radiology component and participating members in the department of Laboratory Medicine and Pathology and the Department of Surgery. The Minnesota Oncology Group joined this cooperative group in order to provide patients with malignant diseases suitable for the cooperative studies conducted by the Cancer and Leukemia Group B. The Minnesota Oncology Group clinical material is composed primarily of patients with acute leukemia, lymphoma, breast cancer, gastrointestinal malignancies, lung cancer and a variety of miscellaneous tumors. The Minnesota Oncology Group consists of established investigators in malignant diseases employing chemotherapeutic agents and hormonal therapies.

The methods of study of diseases are the protocol programs established by the Cancer and Leukemia Group B. The Minnesota Oncology Group initiates new protocol concepts and pilot studies for the treatment of advanced malignant diseases, especially in the areas of lymphoma, leukemia, and solid tumors. The objectives of this research are the development of new chemotherapies and Phase I, Phase II, and Phase III evaluation of chemotherapy in the management of malignant diseases. The development and evaluation of such agents is best provided by cooperative studies that provide large numbers of patients and long-term follow-up. Participation in clinical studies with Cancer and Leukemia Group B provides to that group a large source of clinical patients and investigators experienced in clinical evaluation of chemotherapeutic drugs.

BIBLIOGRAPHIC REFERENCES: Nissen, N.I., Pajak, T.F., Leone, L.A., Bloomfield, C., Kennedy, B.J., Ellison, R.R., Silver, R.T., Weiss, R.B., Cuttner, J., Falkson, G., Kung, F., Bergevin, P.R., and Holland, J.F.: Clinical trial of VP 16 -213 (NSC 141540) i.v. twice weekly in advanced neoplastic disease (Study by the Cancer and Leukemia Group B). Cancer 45: 232-235, 1980.

299. CANCER AND LEUKEMIA GROUP B - CENTRAL OFFICE

Holland, J. F., Glidewell, O. J., Silver, R. T., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

This project provides statistical, operational and coordinating support for the design, conduct, and analyses of, as well as reporting on, clinical trials in the therapy of malignant diseases conducted by the Cancer and Leukemia Group B. It services the cooperative research of 600 scientists in over 75 international hospitals and clinical centers. About 10 new investigations are undertaken each year, while an average of 30 studies are accruing 2000 patients with a variety of cancers and leukemias each year. These studies range in character from the investigation of potential therapeutic effects on new chemotherapeutic agents in advanced cancer patients to the systemic search for curative combinations of surgery, radiotherapy, chemotherapy and immunotherapy in newly diagnosed cancer patients, as well as formal investigation of the psychosocial aspects of cancer and its treatment. Uniform data are provided by these experiments, centrally collected, processed, analyzed and stored, and interim results are regularly reported to participating physicians. These data now form a library of over 20,000 cancer patients treated in accordance with carefully designed experimental therapeutic trials over two decades of Group research.

300. CANCER AND LEUKEMIA GROUP B - RPMI/ SUNYAB

Henderson, E. S., Preisler, H. D., Higby, D. J., Ozer, H., Roswell Park Memorial Inst., Dept. of Medical Oncology, *666 Elm St., Buffalo, New York*, 14263, United States of America

The investigators will conduct clinical therapeutic trials according to strict protocol control in patients with a variety of neoplastic conditions. These studies will be performed using chemotherapy, radiotherapy, and surgery alone or in combination, in concert with other institutional members of the Cancer and Leukemia Group B. All relevant clinical and laboratory information will be documented for analysis by Group statisticians. Local and group pilot studies will be performed. The Pathology Coordinating Center supported by this grant will review the histopathological material submitted on patients referred by all Group members for confirmation of diagnosis and stratification.

BIBLIOGRAPHIC REFERENCES: Drapkin, R., Bjornsson, S., Preisler, H., Higby, D., Getaz, E.P., Henderson, E.S., Caracandas, J., Wallens, W.T., Kuberka, N., Suh, K., and Siddiqi, N.: Adriamycin, Diamminedichloroplatinum and C. Parvum in Non-Small-Cell Bronchogenic Carcinoma. Proc. ASCO, 20:349, 1979. Preisler, H., Browman, G., Henderson, E., Hryniuk, W., and Freeman, A.: Treatment of Acute Myelocytic Leukemia: Effects of Early Intensive Consolidation. Proc. ASCO, 1980.

301. PARTICIPATION IN CANCER AND LEUKEMIA GROUP B

Gottlieb, A. J., Comis, R. L., State University of New York, Upstate Medical Center, School of Medicine, Dept. of Medicine, *766 Irving Ave., Syracuse, New York*, 13210, United States of America

This proposal requests continued funding for institutional participation of the Upstate Medical Center, State University of New York, Syracuse, New York, in the clinical research activities of Cancer and Leukemia Group B. Cancer and Leukemia Group B (CALGB) is a multi-institutional cooperative research group dedicated to the systematic planning, initiation, conduct, analysis, and reporting of research as applied to therapy of patients with malignancy. The scope of interest of CALGB has been broadened to include patients with the so-called 'solid tumors' in addition to leukemia and the 'hematologic' malignancies.

The program in hematologic and solid tumor oncology at the Upstate Medical Center in conjunction with CALGB is an interdisciplinary program, involving the active participation of Surgery, Radiotherapy, Pediatrics, Psychiatry, and Pathology in addition to Medicine. Our activities include broad participation by our faculty, substantial new patient accrual, new study design, pilot studies of new antineoplastic agents and participation and leadership in group administrative and scientific committees. The funding sought in this proposal will provide needed support for continuation of our activities in the areas outlined. With the broadening of our clinical cancer research program as a result of the funding of this proposal, additional salutary effects have resulted in the education of medical students, house officers, nursing staff, as well as the continuing education of our community physicians. In addition, the collaboration with CALGB provides the most recent advances in medical care and medical expertise to an extremely large patient population in the central New York State area.

BIBLIOGRAPHIC REFERENCES: Gottlieb, A.J. and Weinberg, V. Efficacy of Daunorubicin in Induction Therapy of Adult Acute Lymphocytic Leukemia (CALGB 7612). Presented Amer. Soc. Hemat. Dec. 3, 1979. Blood 54:188, 1979, Supplement 1. Ginsberg, S.J., Gottlieb, A.J., Bloomfield, C.D., Blom, J., Crooke, S.T. Combination Chemotherapy with Continuous Infusion, Low Dose Bleomycin. Proceedings of American Society of Clinical Oncology 20:322, 1979.

302. TREATMENT OF ACUTE LEUKEMIA, LYMPHOMAS AND OTHER NEOPLASMS

Cornwell, G. G., Maurer, L. H., McIntyre, O. R., Zacharski, L. R., O'Donnell, J. F., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *N. Hartland Rd., White River Junction, Vermont*, 05001, United States of America

Dartmouth-Hitchcock Medical Center is entering its 21st year as a participating member of Cancer and Leukemia Group B (CALGB). This cooperative group is engaged in the randomized study of various forms of therapy (chemotherapy, radiation therapy, surgery, immunotherapy) in a wide range of neoplastic diseases. This institution continues to be active in its participation in the administration of the central organization, the development of new treatment programs and the entry of patients into existing protocols.

BIBLIOGRAPHIC REFERENCES: Wurster-Hill, D.H., McIntyre, O.R., Cornwell, G.G. III: Chromosome studies in myelomatosis. Virchows Arch. B Cell Path. 29:93-97, 1978. Wurster-Hill, D.H., Cornwell, G.G. III, McIntyre, O.R.: Chromosome aberrations of myeloid and lymphoid cells in cancer patients and family members without evidence of cancer. Cancer Det. and Prev. 2:125-146, 1979.

303. COOPERATIVE STUDY OF ACUTE LEUKEMIA

Bernard, J., Hospital St. Louis, *2 Pl. du Docteur Fournier, 75475 Paris 10, France*

The main objective of this grant is an extended cooperation between CALGB and the Institute of Research on Blood Diseases in studying various diseases.

Many French patients are entered in leukemia and lymphoma protocols.

Adjuvant chemotherapy trials are undertaken in melanomas, osteosarcomas and breast cancers.

304. ACUTE LEUKEMIA COOPERATIVE GROUP B

Kung, F. H., Nyhan, W. L., Yu, A. L., Byfield, J., Utley, J., Pilch, Y. H., Barone, R., Mendelson, J., University of California, San Diego Campus, School of Medicine, Dept. of Pediatrics, *P.O. Box 109, La Jolla, California*, 92093, United States of America

This proposal represents a request to support participation in Cancer and Leukemia Cooperative Group B. This cooperative research is devoted to the investigation of chemotherapeutic approaches to acute leukemia and other human neoplastic diseases. Significant palliation and prolongation of survival has been achieved and contributions have been made in clinical pharmacology. However, the real objective of these studies is the eradication of neoplastic disease by treatment. Studies are being designed to reflect an increasing intensity of attack on the neoplastic cell. The cooperative group technique permits the prompt evaluation in series of reasonable size of promising leads in chemotherapy. These leads or new approaches are often suggested by the results of the group's own work in clinical oncology. Thus, a completed protocol often suggests the new avenues to be explored in new protocols. In addition, protocols are designed to exploit maximally clinical or conceptual advances made in experimental animals. The Division of Hematology-Oncology of the Department of Pediatrics has been a member of Acute Leukemia Group B since 1963. The University of California at San Diego has gradually taken on an interdisciplinary character. Participation of Divisions of Radiation-Oncology, Medicine and Pathology has been active for the past 6 years. Other disciplines including Surgery and Psychiatry are becoming increasingly involved in this work.

305. CANCER AND ACUTE LEUKEMIA GROUP B

Frelick, R. W., DelDuca, V., Wozniak, T. F., Berkowitz, I. M., Samii, S., Egan, J., Benzel, J., Smith, C., Mills, R., Schubert, E., Kyle, A., Knight, M., Wilmington Medical Center, Section of Oncology, *501 W. 14th St., Wilmington, Delaware*, 19899, United States of America

The Wilmington Medical Center Oncology and Hematology groups propose to continue participation in Cancer and Leukemia Group B investigations of cancer treatment, as they have in the past in association with Thomas Jefferson University. These studies include: 1. Phase II studies of new chemotherapeutic agents to determine efficacy in a specific tumor, 2. Phase III studies including not only chemotherapy but also surgery, radiation and immunotherapy, where indicated, to determine the best available treatment, 3. Studies addressing (a) the role of different modes of prevention and/or treatment of hemorrhage and infection in cancer patients, (b) the effect of pathologic and immunologic classification on prognosis and response to treatment, (c) the effect of cancer treatment on the psychological well being of the patient.

We are contributing data on patients entered into the various group protocols as a participating institution in the Cancer and Leukemia Group B. The present application seeks funding (a) to permit continued patient accrual in ongoing protocols, (b) to continue follow-up of patients entered into protocols which have terminated, (c) to collect appropriate biological material and information relevant to such protocols, and (d) to enhance the multidisciplinary approach of this institution in clinical trials.

306. CANCER AND LEUKEMIA GROUP B

Silver, R. T., Nachman, R. L., Cornell University, Medical Center, Cornell Medical College, Dept. of Medicine, *1300 York Ave., New York, New York*, 10021, United States of America

OBJECTIVES: To continue to participate as a member of Cancer and Leukemia Group B (1) studying the natural history of these diseases as modified various experimental therapeutic regimens; (2) to determine effect, extent, and duration of remissions obtained; (3) to determine the relative efficacy of the various agents used; and (4) to promote the best possible treatment of these disorders.

307. CANCER AND LEUKEMIA GROUP B

Cornwell, G. G., Maurer, L. H., North, W. G., Bodwell, J., Dartmouth College, Dartmouth Medical School, Dept. of Medicine, *P.O. Box 833, Hanover, New Hampshire*, 03755, United States of America

Support is sought for technical assistance, equipment and supplies to study plasma neurophysins of oxytocin and vasopressin in patients with small cell carcinoma of the lung who are entered on the protocol presently under development for this disease. Utilizing a sensitive radioimmunoassay developed at Dartmouth to measure these substances in plasma, we have found that approximately two-thirds of patients with this disease have elevated levels of neurophysins at the time of diagnosis and that there is a close correlation between clincial response to therapy and changes in the levels of these substances. The objective of this proposal will be to extend these studies to a group-wide protocol in an effort to characterize differences between secreting and non-secreting tumors to determine, if possible, the optimal time for retreatment after an initial response, and to corralate neurophysin levels with survival.

BIBLIOGRAPHIC REFERENCES: Cornwell, G.G. III, Pajak, T.F., and McIntyre, O.R.: Hypersensitivity reactions to I.V. melphalan during treatment of multiple myeloma: CALGB experience. Cancer Treat. Rep. 63:399-403, 1979.

308. CANCER AND LEUKEMIA GROUP B

Henry, P. H., University of Missouri, Columbia Campus, School of Medicine, Dept. of Medicine, *M228 Medical Sciences, Columbia, Missouri*, 65201, United States of America

We will continue our studies of patients with various forms of malignant diseases utilizing the protocols of Cancer and Leukemia Group B. We will continue to develop a stronger multidisciplinary group of investigators so that a more effective investigative approach to early cancer can be effected both in our institution and in Cancer and Leukemia Group B. The Ellis Fischel State Cancer Hospital is now an integral part of our program.

We have been members of this group for nine years and the association has made some important contributions to the education and training of medical students, medical houseofficers, medical oncology fellows, nurses and social workers.

309. CANCER AND LEUKEMIA GROUP B

Rafla Demetrious, S., State University of New York, Downstate Medical Center, School of Medicine, Dept. of Radiology, *450 Clarkson Ave., Brooklyn, New York*, 11203, United States of America

The chief objective of these studies is the development of therapeutic methods to prolong life for patients with disseminated malignant disease. Patients with leukemia, lymphoma, myeloma, and adult solid tumors will be studied with controlled carefully designed protocols of Cancer and Leukemia Group B.

The objective of the supplementary grant application is to enable the consortium hospitals that form SUNY to satisfy the above objective in an optimum manner.

310. CANCER AND LEUKEMIA GROUP B

Holland, J. F., Wasserman, L. R., Cuttner, J., Aufses, A. H., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

OBJECTIVES: A. To participate in the cooperative studies of the various therapeutic regimens in acute leukemia, chronic leukemia, multiple myeloma, the lymphomas, breast cancer, lung cancer, gastrointestinal cancer and other adult solid tumors to be studied by the Cancer and Leukemia Group B. B. The toxicity and therapeutic range of new agents will be determined in Phase I studies; the frequency, extent and duration of remission with new agents will be evaluated in the Phase II studies; and the relative efficacy of various therapeutic regimens at different stages of the disease will be determined in Phase III studies. C. To complete our development into a multidisciplinary group with full participation of surgeons and radiotherapists. This goal has been achieved with the participation of breast surgeons. We plan to extend this participation to general surgeons. D. To develop and participate in studies using immunotherapeutic agents in neoplastic disease states. E. To utilize the case material for the cooperative chemo- and radiotherapy studies for ancillary investigations of some of the biological, biochemical and immunological aspects of the neoplastic diseases under study.

BIBLIOGRAPHIC REFERENCES: Kyle, R.A., Gailani, S., Seligman, B.R., Blom, J., McIntyre, O.R., Pajak, T.F. and Holland, J.F.: Multiple Myeloma Resistant to Melphalan Treatment with Cyclophosphamide, Prednisone and BCNU. Cancer Treat. Rep. 63:1265-1269, 1979. Chahininan, A.P., Mandel, E.M., Holland, J.F., Jaffrey, I.S. and Terstein, A.S.: MACC (methotrexate, adriamycin, cyclophosphamide and CCNU) in Advanced Lung Cancer. Cancer 43: (No. 5) 1590-1597, 1979.

311. CANCER AND LEUKEMIA GROUP B

Copper, M. R., Wake Forest University, Bowman Gray School of Medicine, Dept. of Medicine, *300 S. Hawthorne Rd., Winston Salem, North Carolina*, 27103, United States of America

The Bowman Gray School of Medicine, through the leadership of Dr. Charles L. Spurr, has participated in Cancer and Leukemia Group B since 1958. This institution has evolved a multidisciplinary approach to the cancer problem and serves as a referral area for an excess of 3,000,000 people. Twelve percent of hospital admissions are directly placed on the hematology/oncology service and 25 percent of total admissions are related to the cancer problem. The care of these patients is carefully coordinated between the Sections of Hematology/Oncology, Radiation Therapy, General Surgery, and Gynecological Oncology. In addition to a full complement of professional staff, we have developed a strong supportive personnel in cancer chemotherapy, data collection, statistical analysis, and special oncological nursing care. The specific aims are: (1) To participate in the development of prospective randomized trials of improved therapies for malignant disease. (2) To participate in existing well-planned clinical trials testing new designs of multidisciplinary therapy. (3) To improve the treatment and classification of neoplastic disease by more thorough morphological, biochemical, and immunological studies of tissue specimens. (4) To develop improved supportive therapy of the cancer patient to sustain and/or prevent toxicity of multimodality therapy. (5) To develop an improved system of data collection and management to improve patient evaluability. (6) To disseminate improved therapies for neoplastic disease to our regional referral system via the Piedmont Oncology Association.

312. ACUTE LEUKEMIA COOPERATIVE STUDY GROUP B

Haurani, F. I., Thomas Jefferson University, Jefferson Medical College, Dept. of Medicine, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

The objective of this study is to participate in the studies of Cancer and Leukemia Group B. The aim of this group is (1) to screen new chemotherapeutic agents in patients with cancer (Phase I study), (2) to explore the clinical pharmacology of known effective drugs (Phase II studies). This consists of optimal dose, frequency of administration, sequence of administration, combination of agents and route of administration. Again, emphasis will be on the importance of consolidation and reinduction in the duration of remission and survival.

Besides chemotherapeutic agents, interdisciplinary programs have been developed to include radiotherapy, immunotherapy, anti-viral chemotherapy, surgery and psychiatry. Ancillary treatment which includes platelet transfusion, granulocyte transfusion and sterile environment and antibiotics will be evaluated.

We have, presently, the following centers working with us: (1) Wilmington Medical Center, (2) Albert Einstein Hospital/Northern Division, (3) Albert Einstein Hospital/Daroff Division, (4) Cooper General Hospital, (5) John F. Kennedy Hospital, (6) Lankenau Hospital, (7) Medical College of Penn, (8) Philadelphia Naval, (9) Portsmouth Naval, (10) Our Lady of Lourdes Hospital, (11) Woodbury Memorial Hospital.

BIBLIOGRAPHIC REFERENCES: Haurani, F.I., and Masse, A.T.: Serine hydroxymethyltransferase and the stimulated human lymphocyte. J. of the R.E.S. 21:231-235, 1977. Maurani, F.I.: Folate analogues and thymidylate synthetase of the PHA stimulated human lymphocyte. J. of the R.E.S., Dec. 1977.

313. CANCER AND LEUKEMIA GROUP B

Leventhal, B. G., Johns Hopkins University, School of Medicine, Dept. of Pediatrics, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

We plan to continue our active participation in CALGB protocols. Patient accrual will continue at least at the present level and may well increase as the activity of the pediatric subcommittee increases and more pediatric protocols are activated by the group as a whole. Dr. Kaizer is involved in planning a new non-Hodgkin's lymphoma protocol for the group.

The immunotherapy subcommittee is exploring possible agents other than intradermal MER for immunotherapy and new protocols will soon be emerging.

314. ACUTE LEUKEMIA GROUP B

Jones, B., West Virginia University, School of Medicine, Dept. of Pediatrics, *Morgantown, West Virginia*, 26506, United States of America

The efficacy of various chemotherapeutic agents in the treatment of neoplastic disease is being investigated. As a cooperative member of Acute Leukemia Group B we are following specific protocols in the treatment of acute leukemia, lymphomas, multiple myeloma, and adult and childhood solid tumors. Drugs with known activity in these disorders are being used in an attempt to determine the most effective dosage and route of administration. Combinations of drugs are being investigated for possible synergistic action. New agents which appear effective in animal screens are tried in appropriate situations to determine their activity and tumor spectrum in man. Multidisciplinary protocols involving surgery, radiotherapy, and chemotherapy are being developed for many tumors to be implemented at the time of diagnosis in an attempt to increase the survival and potentially to cure the patient.

BIBLIOGRAPHIC REFERENCES: Jones, B., et al.: Optimal Use of L-Asparaginase (NSC 109229) in Acute Lymphocytic Leukemia. Med. and Peds. Oncology, 3: 387-400, 1977. Wiernick, P.H., Jones, B., Weinberg, V., Holland, J.F., for Cancer and Leukemia Group B. Present day results in your patients with Acute Nonlymphocytic Leukemia (ANLL) Second International Symposium on Therapy of Acute Leukemias. December 8-10, 1977 (Rome).

315. CANCER AND ACUTE LEUKEMIA GROUP B

Leone, L. A., Glicksman, A., Rege, V., Schilling, A., Gerken, M., Vohr, F., Kaan, S., Colbert, M., Vreeland, F., Rhode Island Hospital, Dept. of Medical Oncology, *593 Eddy St., Providence, Rhode Island*, 02903, United States of America

Supplement application to continuation grant application no. 2R10-CA08025-16, which supports participation of Rhode Island Hospital Oncology Group (Medical Oncology, Radiation Oncology, Immunology, Surgery, Pediatric Oncology). A fully integrated multidiscipline activity to implement participation of the Rhode Island Hospital in Cancer and Acute Leukemia Group B is proposed. The group takes a fully active role in origination of new protocols, establishment and implementation of multiple pilot studies, leadership of CALGB committees.

316. CANCER AND LEUKEMIA GROUP B

Schein, P. S., Hoth, D. F., Smith, F. P., Macdonald, J. S., Woolley, P. V., Neefe, J., Dritschilo, A., Georgetown University, School of Medicine, Dept. of Medicine, *3800 Reservoir Rd. N.W., Washington, District of Columbia*, 20007, United States of America

The purpose of this project is to establish a multimodality approach to the therapy of adult cancers, as coordinated under the cooperative group, CALGB. This effort will be directed towards continued participation in the conceptual design and conduct of CALGB protocol studies for solid tumors and hematologic malignancies. This multimodality approach will include the integrated efforts of medical oncologists, radiation therapists, oncologic surgeons and immunologists and psychiatrists.

317. CANCER AND LEUKEMIA GROUP B

Raich, P. C., Watne, A. L., Frich, J. C., Rogers, J. S., Walker, B. K., Subramanian, V. P., Hendrick, A. M., Harris, H. H., West Virginia University, School of Medicine, Dept. of Medicine, *Morgantown, West Virginia*, 26506, United States of America

Cancer and Leukemia Group B is a cooperative group of institutions dedicated to finding better means of treating various types of malignancies utilizing a multimodality approach. For newly diagnosed patients treatment protocols are designed which incorporate the most effective known modalities including surgery, radiotherapy, and chemotherapy. The aim of these studies is to increase the survival and, potentially, to cure the patient. New investigational agents are used in patients with more advanced cancer to determine activity and therapeutic spectrum in man. In addition, some of the psychosocial aspects of cancer and cancer treatments are also under study. In this effort physicians and other staff at West Virginia University will continue to participate actively in the various activities of Cancer and Leukemia Group B. Faculty from the Division of Hematology/Oncology and the Departments of Surgery, Radiation Oncology, Pathology and Psychiatry have developed an interdisciplinary approach to the evaluation and care of cancer patients. The success of this effort is reflected in the steadily increasing number of patients entered into protocol studies over the past 20 months. Further development of institutional resources, collaborative programs with satellite centers, and community outreach within the State of West Virginia and adjoining regions are expected to provide additional numbers of patients eligible for protocol studies.

318. ACUTE LEUKEMIA GROUP B CANCER CHEMOTHERAPY PROTOCOL (HUMAN)

Henry, P. H., University of Missouri, Columbia Campus, School of Medicine, Dept. of Medicine, *M228 Medical Sciences, Columbia, Missouri*, 65201, United States of America

This is part of a broader project. A summary of this subproject is not available.

B. EASTERN, SOUTHEAST AND SOUTHWEST COOPERATIVE GROUPS (ECOG, SEOG AND SWOG)

319. EASTERN COOPERATIVE ONCOLOGY GROUP

Horton, J., Union University, Albany Medical College, School of Medicine, Dept. of Medicine, *47 New Scotland Ave., Albany, New York*, 12208, United States of America

This research grant relates to the part of the National Cancer Plan concerned with the improvement of treatment of patients with cancer. The investigators will participate in the activities of the Eastern Cooperative Oncology Group (ECOG) in the development, performance, evaluation and reporting of well-performed, scientifically controlled, cooperative clinical studies on patients with a wide variety of solid tumors as well as lymphomas and Hodgkin's disease, myeloma, and acute and chronic leukemia. A variety of treatment modalities will be incorporated, including surgery, radiation therapy, chemotherapy, and immunotherapy. Increased emphasis is placed on multimodality programs and adjuvant treatment studies. In addition to the Group studies as described, the investigators will assist in the administration of the Group and will perform pilot studies that can lead to groupwide testing. Important secondary benefits of these studies are excellence of patient care and improved training of medical personnel which will ensue.

BIBLIOGRAPHIC REFERENCES: Lempert, M., MacDowell, R.T., Karmody, A., Cunningham, T.J., Sponzo, R.W., Ruckdeschel, J.C., and Horton, J. Vascular Access for Cancer Chemotherapy. Cancer. In press, 1979. Caradonna, R., Paladine, W., Ruckdeschel, J.C., Goldstein, J.C., Olson, J., Jaski, J., Silvers, S., Hillinger, S., and Horton, J. Methotrexate, Bleomycin and High Dose Cis-Platinum for Advanced Epidermoid Carcinoma of the Head and Neck. Cancer Treatment Reports. In press. 1979.

320. EASTERN COOPERATIVE ONCOLOGY GROUP

Ballard, H. S., Hamilton, L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *1st Ave. at E. 24th St., New York, New York*, 10010, United States of America

During 1979 we actively followed 35 patients randomized either in 1979 or previously to various Eastern Cooperative Oncology Group (ECOG) protocols. Twenty-four previously treated patients are not presently receiving chemotherapy and are under observation. Two patients are currently receiving chemotherapy (one patient randomized to ECOG no. 3476 and another to ECOG no. 2479) according to protocol. The remaining seven patients have required chemotherapy off protocol either because of relapse or initial chemotherapy failure. Two patients expired during 1979 (one patient with favorable non-Hodgkin's lymphoma (ECOG no. 4477) and one patient with active chronic lymphocytic leukemia (ECOG no. 3476)). Ten patients with indolent CLL are under observation. Of five patients with active CLL, one has completed therapy and is under observation. Three are currently receiving chemotherapy and one expired during an episode of sepsis perhaps related to total body irradiation. Two patients with multiple myeloma are receiving chemotherapy, two are under observation and one expired from an unrelated cause. One patient randomized to ECOG protocol no. 2476 (Acute Myeloblastic Leukemia) has relapsed and is currently receiving therapy. Four patients with Hodgkin's disease are currently under observation and not receiving therapy. Six patients with favorable non-Hodgkin's lymphoma are being followed (4 under observation and not receiving therapy, and 2 receiving chemotherapy). Three patients with unfavorable non-Hodgkin's type lymphoma are under observation, in clinical remission and one patient with an unfavorable non-Hodgkin's lymphoma (mycosis fungoides) is currently receiving chemotherapy.

321. EASTERN COOPERATIVE ONCOLOGY GROUP

Ezdinli, E. Z., Hindo, W. A., Gracz, K., Wasser, L., Jovanovic, L., University of Health Sciences, Chicago Medical School, Dept. of Medicine, *2020 W. Ogden Ave., Chicago, Illinois*, 60612, United States of America

The ECOG Program of the University of Health Sciences/The Chicago Medical School has continued as an active participating institute with an annual accrual rate of around 100 patients into a wide spectrum of ECOG protocols.

The program remains multi-disciplinary and has a basic research component studying the incidence and the significance of a plasma rosette inhibiting factor first noted in active Hodgkin's disease patients and occasionally observed also in other types of malignancy. Institutional chemotherapy pilot studies are also pursued.

The faculty has been expanded and methods for increasing patient accrual by satellite institutes are being explored.

322. EASTERN COOPERATIVE ONCOLOGY GROUP

Mittelman, A., Douglass, H. O., Nava, H., Vincent, R., Sako, K., Creaven, P., Roswell Park Memorial Inst., Dept. of Surgical Oncology, *666 Elm St., Buffalo, New York*, 14263, United States of America

Roswell Park Memorial Institute's participation in the Eastern Cooperative Oncology Group has stressed areas of protocol development, integration of multimodality therapy, cancer control at a community level and data quality control. Roswell Park group members play important roles in the Surgical Committee, GI Committee, Cancer Control Committee and Quality Control Committee of the Eastern Cooperative Oncology Group. Roswell Park also provides drug study chairmen for three protocols. The Outreach Program now involves active participation from four hospitals.

323. SOUTHEASTERN CANCER STUDY GROUP

Keller, J. W., Huguley, C. M., Vogler, W. R., Winton, E. F., Moore, M. R., Heffner, L. T., York, R. M., Corley, C. C., Nixon, D., Emory University, School of Medicine, Dept. of Medicine, *1364 Clifton Rd. N.E., Atlanta, Georgia*, 30322, United States of America

OBJECTIVES: To participate in the initiation, development and conduct of clinical research studies of the Southeastern Group and to foster acceptance and cooperation of surgical, medical and radiation oncologists in multidisciplinary trials. To design innovative, scientifically sound, clinical research studies which will improve quality of management of hematologic and solid tumor malignancies. To assist in defining and refining staging, management and evaluation procedures to accurately, uniformly and adequately identify and analyze patient populations. To place sufficient numbers of appropriate, well studied patients on Group studies so that the answers to questions posed will be promptly available and scientifically sound. To report well documented results to the profession with accuracy and dispatch. To play a major role in committee leadership, participation in committee work and to take an active part in the design of and responsibility for carrying out of Group protocols. To conduct ancillary and pilot studies which explore and develop new methods of diagnosis, treatment and evaluation which are consonant with the long-term goals of the Group. To provide indoctrination, education, training and practical experience in cancer clinical trials to fellows, house staff, medical students, nurses, physicians' assistants and other allied health personnel. To provide a service of disseminating information on current progress in clinical cancer research and to help bridge the gap between medical centers and community physicians.

BIBLIOGRAPHIC REFERENCES: Israili, A. H., Soliman, A. M., Cunningham, R.F., Plowden, J. F., and Keller, J. W. The Interaction of Methotrexate and Probenecid in Man and Dog. Proc. AACR/ASCO 194, 1978. Kann, H.E. Definition of Carbamoylating Activity as a Major Basis for the Radiation Synergism of Nitrosoureas. Clinical Res. 26 (3): 438A, 1978.

324. COOPERATIVE STUDIES IN CANCER THERAPY

Silberman, H. R., Seigler, H. F., Shingleton, W., Noell, T., Cox, E., Moore, J., Fay, J., Woodward, K., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina*, 27710, United States of America

Support is requested for proposed participation within the Southeastern Cancer Study Group's cooperative clinical trials, most of which are conducted in 3 phases.

Phase I studies will be studies of toxicity, of new dosage schedules or combinations of drugs or combined modalities. Phase II studies, sometimes randomized, will evaluate effectiveness of a specific treatment plan in a series of patients with a specific disease, emphasizing the signal tumors and melanoma. Phase III studies will be randomized comparisons of two or more treatment regimens in solid tumors, malignant lymphomata and hematologic malignancies, using combinations of surgery, x-irradiation, drugs and immunomanipulation where appropriate.

Ancillary and pilot studies at this and other institutions will continue. These are: 1) Preliminary investigations which may later justify a group effort; 2) basic investigations to elucidate mechanisms of action; 3) efforts at better methods of data evaluation, techniques of measuring response, and stratifying categories of patients with a specific disease; and 4) new approaches to supportive care. Emphasis is upon thorough planning, careful analysis of data, and statistically sound evaluation, all of which improves patient care, and training of new physicians-investigators.

BIBLIOGRAPHIC REFERENCES: Logue, G.L., Kurlander, R., Pepe, P., Davis, W. and Silberman, H.R.: Antibody-dependent Lymphocyte-mediated Granulocyte Cytotoxicity in Man. Blood, 51:97, 1978. Laszlo, J., Jones, R., Silberman, H.R. and Banks, P.: Splenectomy for Felty's Syndrome. Arch. Inter. Med. 138:597, 1978.

325. SWOG 7903/7961, ADVANCED (STAGES III AND IV) HODGKIN'S DISEASE REMISSION INDUCTION WITH CHOP

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

The object of this study is to test a commonly used four drug combination, CHOP, for remission induction within Hodgkin's disease. All of the agents used in the CHOP regimen are active in Hodgkin's disease as single drugs. The four drug combination will be used for remission induction in prior MOPP failures who have had no prior anthracycline. This is a potentially very effective non-cross resistant combination. In addition to this, a two institution pilot study will be done in an attempt to determine the activity of this four drug combination in previously untreated patients with Hodgkin's disease.

326. SWOG-7963, PHASE II PILOT STUDY OF M-AMSA IN MELANOMA, MYELOMA, LYMPHOMA, OAT CELL LUNG CARCINOMA AND BREAST CANCER

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

This is a pilot study in which m-AMSA, a newly discovered antitumor agent, will be used to treat refractory malignant melanoma, multiple myeloma, lymphoma, oat cell carcinoma, and breast cancer. This compound has been through extensive phase I clinical trials and has been demonstrated to have activity in those tumor categories. Only patients who have failed on protocols of higher priority will be eligible for study of this phase II agent.

327. CHEMOTHERAPY OF ADVANCED MALIGNANCIES - SWOG 7524

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

Chemotherapy of Advanced Malignancies - The objectives of the protocols herein contained are to improve the results of treatment for patients with non-Hodgkin's lymphomas and squamous carcinoma of the head and neck. In the former situation a prospective, randomized comparison of two different combination chemotherapy regimens and one chemoimmunotherapy program is to be carried out. In the latter, patients are to be randomized between methotrexate alone, a standard form of treatment, and a three-drug combination combining Methotrexate and 2 other active drugs. Comparisons will be made based on response rate, toxicity and survival data. As soon as a conclusion can be reached regarding superiority of a particular regimen, these studies will be closed.

SWOG 7524 - To compare the effectiveness of chemotherapy alone (adriamycin-cyclophosphamide) vs. chemoimmunotherapy (adriamycin-cyclophosphamide plus BCG) for remission induction in patients with Stage III and IV ovarian and endometrial carcinoma who have had no previous cytotoxic chemotherapy. To test the effectiveness of continued chemoimmunotherapy vs. chemotherapy in maintaining complete remissions (documented) achieved during the initial 12 month induction therapy. To test the effectiveness of continued chemoimmunotherapy vs. chemotherapy in inducing complete remissions or maintaining partial remissions in patients with occult disease at the time of restaging for complete response or in patients achieving only partial clinical remission during the initial 12 month induction therapy. This study was activated in October of 1974 and closed in October of 1976. All patients from this center were entered into the study. 154 were entered groupwide. The data showed that adriamycin-cyclophosphamide plus BCG was better than adriamycin-cyclophosphamide alone in terms of actuarial survival. No further case entries are anticipated.

328. CANCER CHEMOTHERAPY AND IMMUNOLOGY PROTOCOLS (SWOG PROTOCOLS 7518, 7520, 7580, 7406, 7424/25, 7435, 7475)

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

7518: This study for Stage IIIA and B Hodgkin's disease has had a total of 129 patients entered in the cooperative group and no patients have been entered from San Antonio. The study shows that disease-free and overall survival of the two regimens are essentially equivalent.

7520: No patient entries from this institution on this study. This study has been closed for further patient entry.

7580: This study for the immune evaluation of lymphoma patients in unmaintained remission, patient entries from this institution on the study, is closed for further case accrual.

7406: Five patients entered from this institution and there are a total of 392 cases entered groupwide. This study has been closed for further case accrual. Overall response rate is 69% with the complete response rate from MOPP-Bleo at 64% and the MOP-BAP combinations - 76%.

7424/25: This study employing combination chemoimmunotherapy for patients with disseminated malignant melanoma has no case entries from this hospital. The study is now closed.

7435: No patients have been entered into this study from this hospital. The study is now closed.

7475: One patient has been entered into this study from this institution and the groupwide study is now closed; the manuscript is in preparation.

329. SOUTHWEST ONCOLOGY GROUP PROTOCOL 7823/24/25/26, ROAP-ADOAP IN ACUTE LEUKEMIA, PHASE III

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

This study is designed for patients over the age of 15 who have been diagnosed as having acute leukemia and who have an absolute infiltrate of 50% leukemic cells or greater, or who have a 30 to 49% absolute infiltrate with evidence of progression. Patients with significant cardiovascular disease are excluded as are patients with serious liver or renal dysfunction. A random half of the patients will receive the four-drug combination of rubidazone, oncovin, ARA-C and prednisone for remission induction. Among those patients who achieve complete remission, three courses of intensive consolidation therapy will be administered with reduced dose of anthracycline and ARA-C. After consolidation the patients will all receive standard five-day OAP maintenance. Patients still in remission nine months after complete remission will be randomized to receive three cycles of POMP as late intensification versus continued maintenance OAP to determine if this approach will improve disease-free survival. Twelve months after complete remission all chemotherapy will be stopped. Patients will be randomly assigned at that point to receive immunotherapy maintenance with Levamisole or no further treatment.

One patient has been entered on this study and remains in continuous complete remission for over one year.

330. SW ONCOLOGY GROUP - CHEMOTHERAPY OF CHILDHOOD ACUTE LEUKEMIA AND SOLID CA

Vietti, T. J., Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

This is part of a broader project. A summary of this subproject is not available.

331. SOUTHWEST ONCOLOGY GROUP, ALLEGHENY GENERAL HOSPITAL

Pugh, R. P., Schiffer, L. M., Zidar, B. L., Pfrimmer, W. J., Concannon, J. P., Hughes, J., Allegheny Singer Research Corp., Division of Medical Oncology, *320 E. North Ave., Pittsburgh, Pennsylvania*, 15212, United States of America

The primary research objective of this request is to conduct collaborative chemotherapy trials of the Southwest Oncology Group (SWOG) according to the various cancer disciplines of the Allegheny General Hospital. In addition to the implementation of SWOG protocols after appropriate institutional review for the protection of human rights, existing research resources of the participating investigators will be applied to SWOG activities, largely through SWOG disease and discipline oriented committee participation. Of special import will be the development of a tumor biology-cell kinetics program to access cell kinetics information on a pilot basis in appropriate SWOG protocols. The logistics of implementing the use of cell kinetics studies in a limited number of participating institutions by employing a common cell kinetics kit will be tested. In addition, pilot chemotherapy protocol design will be correlated with kinetics data. Special contribution to SWOG activities is also anticipated by in depth review of non-Hodgkin's lymphoma Group pathologic material under the direction of the Lymphoma Subcommittee Chairman at Allegheny General Hospital.

332. SOUTHWEST ONCOLOGY GROUP (PEDIATRICS)

Van Eys, J., Cangir, A., Sutow, W. W., Sullivan, M. P., Jaffe, N., Ried, H. L., Culbert, S. J., Frankel, L. S., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Pediatrics, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

Investigative clinical therapeutic studies in children with acute leukemia, malignant lymphoma, histiocytosis X, and malignant solid tumors (brain tumors, neuroblastoma, Wilms' tumor, osteogenic sarcoma, Ewing's sarcoma, soft tissue sarcoma, and miscellaneous malignant neoplasms) are conducted in four areas: (a) Phase I coordinated studies of human pharmacologic and toxicologic aspects of new anticancer agents and new combinations and dosage regimens; (b) Phase II systematic investigations of the effectiveness of individual anticancer agents or treatment programs in specific tumors; (c) Phase III comparative evaluations of selected drugs and/or therapy regimens; and (d) specific laboratory investigations into immunology and clinical pharmacology. The functioning cooperative group study mechanism is utilized to increase the size of the study populations and to shorten the duration of the study.

Independent investigative probes are undertaken to explore leads resulting from or directed toward group studies. Several intergroup and national studies, ongoing and projected (National Wilms' Tumor Study, Intergroup Rhabdomyosarcoma Study, Intergroup Ewing's Sarcoma Study, Hepatoma Study, Hodgkin's Disease Study) are included.

This research will be executed in an integrated multimodal manner. Attention will be given to centralized data management for the individual specialities of pediatrics, surgery, radiotherapy, pathology and laboratory support. Special attention will be given to clinical pharmacology and the immunological investigation required for optimal execution of current protocols employing high dose methotrexate or protocols requiring classification of lymphoid malignancies in order to establish proper therapy assignment.

333. SOUTHWEST ONCOLOGY GROUP (CLINICAL)

Ragab, A. H., Lui, V. K., Kim, T. H., Woodruff, R. D., Woodard, J. R., O'Brien, M. S., Whitehead, T., Haley, C. L., Simmons, G., McMillan, A., Emory University, School of Medicine, Dept. of Pediatrics, *1364 Clifton Rd. N.E., Atlanta, Georgia*, 30322, United States of America

The Pediatric Hematology/Oncology Division at Emory University is the only patient cancer center within a radius of 180 miles. This center offers multimodal therapy to children with malignant disorders. Although this division was inactive for a period of one year, it is currently very active and caring for approximately 250 children with malignant disorders. This division is unique in that it cares for private patients at Emory University Clinic and at the Henrietta Egleston Hospital for children and for indigent patients at Grady Memorial Hospital. The division cares for children in the Atlanta area (population 1.7 million), the state of Georgia, and other neighboring states including North and South Carolina and Alabama. This center is the second largest contributor to the pediatric division of SWOG.

In collaboration with the Southwest Oncology Group, the center offers access to new intensive therapeutic regimens and experimental agents to approximately 250 children with malignant diseases. An extensive ancillary study, both at the clinical and the preclinical level, is under way in parallel with the Southwest Oncology Group studies in children with malignant disorders. Thus, the bone marrow culture technique for the growth of granulopoietic and erythroid progenitor cells is being used to evaluate the effects of chemotherapeutic agents on granulopoiesis and erythropoiesis in man. The same technique is being applied to investigate the cryopreservation of human bone marrow cells and tumor cells. We hope that these studies will offer new insight into the effect of chemotherapeutic agents and the management of children with malignant disorders.

BIBLIOGRAPHIC REFERENCES: Crist, W., Ragab, A.H., and Ducos, R.: Lymphoblastic conversion of chronic myelogenous leukemia. Ped. 61(4):560-563, April, 1978. Crist, W., Ragab, A.H., Moreno, H., Pereira, F., Foster, J.C.: Granulopoiesis in chronic myeloproliferative disorders in children. Ped. 61(6):889, June, 1978.

334. SOUTHWEST ONCOLOGY GROUP

Freireich, E. J., McCredie, K. B., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Developmental Therapeutics, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

Development of improved therapy for adult leukemia still serves as the primary objective of this research. Our aim is to be able to get our leukemia patients to stay in remission for longer periods of time. Important research has been developed and the individual drugs have been very successful in the treatment of adult leukemia. Perhaps even more important than the identification of individual drugs has been the development of important principles of treatment. In the adult forms of leukemia, we have a spectrum in degrees of malignancy which are extraordinarily broad. These range from the highly undifferentiated malignancies which resemble stem cell tumors such as acute lymphoblastic leukemia all the way to the chronic leukemia diseases such as chronic granulocytic leukemia where hypertrophy of what appears to be completely normal differentiation is the early manifestation of malignancy. Particularly in the case of the myeloid leukemias there is now an opportunity to investigate malignancy occurring throughout all phases of the development of the cells that differentiate from the organ. Techniques for prolongation of remission, once achieved, include the effectiveness of immunological adjuvant therapy. The present grant supports the work of the Chairman of the Adult Leukemia Committee of the Southwest Oncology Group and draws upon the expertise within the Department of Developmental Therapeutics to develop new research leads, conduct pilot studies and participate in the groupwide studies of the Southwest Oncology Group.

335. SOUTHWEST ONCOLOGY GROUP

Kung, F. H., Schwartz, D. B., Nyhan, W. L., Bach, P. B., Koenig, H. M., University of California, San Diego Campus, School of Medicine, Dept. of Pediatrics, *P.O. Box 109, La Jolla, California*, 92093, United States of America

This proposal represents a request to support participation in Southwest Oncology Group. This cooperative research is devoted to the investigation of chemotherapeutic approaches to leukemia and other human neoplastic diseases. Significant palliation and prolongation of survival have been achieved and contributions have been made in clinical pharmacology. However, the real objective of these studies is the eradication of neoplastic disease by treatment. Studies are being designed to reflect an increasing intensity of attack on the neoplastic cell. The cooperative group technique permits the prompt evaluation in series of reasonable size of promising leads in chemotherapy. These leads or new approaches are often suggested by the results of the group's own work in clinical oncology. Thus, a completed protocol often suggests the new avenues to be explored in new protocols. In addition, protocols are designed to exploit maximally clinical or conceptual advances made in experimental animals. The Division of Hematology-Oncology of the Department of Pediatrics has been a member of a cancer chemotherapy cooperative group since 1963. The University of California at San Diego has gradually taken on an interdisciplinary character. Radiation-Oncology, Surgery and Pathology have participated actively for the past 6 years. Other disciplines including Immunology, Pharmacology, Cell Kinetics and Psychiatry are becoming increasingly involved in this work.

336. SOUTHWEST ONCOLOGY STUDY GROUP - SUPPLEMENT

Crist, W. M., Roper, M., Dearth, J. C., Cooper, M. D., University of Alabama in Birmingham, School of Medicine, Dept. of Pediatrics, *1919 7th Ave. S., Birmingham, Alabama,* 35233, United States of America

Increased support is requested to permit full participation of the 19 former ALGB, Pediatric Division members who have recently joined the Pediatric Division of the SWOG to participate in the ongoing immunologic evaluation of pediatric patients with acute lymphocytic leukemia. Specifically, these additional funds will be used to prepare highly purified antibodies to detect cytoplasmic and surface immunoglobulins within or upon lymphoblasts, for other needed supplies as specified, and to support the additional technical personnel required.

337. TREATMENT OF CHILDHOOD CANCER

Freeman, A. I., Roswell Park Memorial Inst., Dept. of Pediatrics, *666 Elm St., Buffalo, New York,* 14263, United States of America

The current success in treating a number of types of childhood cancer is the result, in large part, of therapeutic research conducted by the cooperative pediatric cancer groups. Because most childhood cancers are rare, it is only through this mechanism that adequate numbers of patients can be accrued in reasonable lengths of time and that therapeutic questions can be answered. We will participate in the pediatric division of the Southwest Oncology Group (SWOG) so that our patient population can be used to answer treatment questions which would be impossible to answer were we to conduct only single institution studies.

There are some pediatric solid tumors for which the accrual, even in cooperative groups, is insufficient for meaningful therapeutic studies to be conducted. However, a number of intergroup studies are presently active and we plan to participate in these studies through the pediatric division of SWOG. Specifically, we will continue to enter patients on the National Wilms' Tumor Study, the Intergroup Ewing's Sarcoma Study, the Intergroup Rhabdomyosarcoma Study and the Intergroup Hodgkin's Disease Study. The diseases included in these intergroup studies are those which most commonly demand an interdisciplinary approach. We are strongly committed to this approach and have a good working relationship with the necessary cooperating specialities, including Radiation Therapy, Pediatric Surgery, Neurosurgery and Orthopedic Surgery.

As more children enter long-term remissions from their diseases, the identification, treatment and potential for prevention of complications of therapy have become significant areas for research. Our major areas of investigation include population based studies of major complications of radiation therapy and chemotherapy, investigations into the treatment and prevention of varicella-zoster infection in immunosuppressed patients and evaluation of the acute and long-term effects of radiation therapy and chemotherapy on various committed stem cell pools and the peripheral blood and bone marrows.

C. CHILDREN'S CANCER STUDY GROUP (CCSG)

338. CHILDREN'S CANCER STUDY GROUP A

Lahey, M. E., Utah Higher Education System, University of Utah, School of Medicine, Dept. of Pediatrics, *1400 E. 2nd S., Salt Lake City, Utah,* 84112, United States of America

The above-named professional personnel propose to collaborate with other members of CCSG as well as with other members of other cooperative study groups, in research on leukemia, malignant solid tumors and closely related disorders in children. The chief purpose of the CCSG is to cooperate in several aspects of research in malignant disease in children (i.e., the natural history, epidemiology) and in particular to develop, evaluate and improve methods of diagnosis, prognosis and treatment of malignant disease in children.

Special emphasis will be placed on the study of new combinations and new schedules of already established chemotherapeutic agents as well as on the evaluation of new anti-cancer agents and new modalities of therapy.

The Principal Investigator is Chairman of the Histiocytosis Committee and has recently received approval by CIB of a new protocol designed to study this disorder in depth with particular attention to clinical and histologic features of prognostic significance, improved therapy and comprehensive immunologic evaluation. The prognostic significance of certain clinical features developed by CCSG has been tested and acclaimed by other chemotherapy groups.

339. CHILDREN'S CANCER STUDY GROUP A

Shahidi, N. T., University of Wisconsin, Madison Campus, Medical School, Dept. of Pediatrics, *307 N. Charles St., Madison, Wisconsin,* 53706, United States of America

The members of the Children's Cancer Study Group, using mutually agreed upon protocols, conduct clinical investigations regarding optimal therapy of children with leukemia and solid tumors. The aim of such protocols is to evaluate therapeutic regimens, often combining surgery, radiotherapy, and chemotherapy, in an effort to increase disease-free survival and improve the cure rate of these illnesses. In addition, information regarding supportive care, use of blood products, toxicity, and survival is gathered and evaluated.

340. THE CHILDRENS CANCER STUDY GROUP

Finklestein, J. Z., University of California, Los Angeles Campus, Los Angeles County Harbor General Hospital, *1000 W. Carson St., Torrance, California,* 90509, United States of America

OBJECTIVE: The purpose of this project is to continue and expand the active participation of Harbor General Hospital and affiliated institutions in all phases of the Children's Cancer Study Group.

The research involves a multi-disciplinarian approach to the clinical investigation of childhood cancer with special emphasis on chemotherapy of Acute Leukemia and Solid Tumors of Childhood with collaborative protocols developed by the Children's Cancer Study Group. We will continue in the study and the treatment of pediatric oncologic disorders by means of Phase I, II, and III Protocols. In addition, pertinent questions regarding natural history, treatment and epidemiology of childhood cancer will be investigated.

APPROACH: The results of therapies are recorded by the institutions' pediatric oncology staff, including Data Managers, and Protocol Nurse Coordinators, supervised by Sub-specialists in Pediatric Oncology. Information is forwarded to the Operations Office for detailed statistical analysis.

The ultimate benefit is that the investigation involves controlled clinical trials in leukemia and solid tumors of childhood, controlled evaluations of newly developed therapeutic agents and controlled studies of the effects of immunotherapy and immuno-suppression. Children participating in this project will benefit by being offered the most up-to-date methods of diagnosis, treatment and management of their disorders. The program seeks a scientific approach to a comprehensive, therapeutic investigation of childhood cancer.

341. CHILDREN'S CANCER STUDY GROUP

Nesbit, M. E., Krivit, W., Coccia, P. F., Ramsay, N. K., O'Leary, M., Golembe, B., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Pediatrics, *1305 Mayo, Minneapolis, Minnesota,* 55455, United States of America

The specific goals of the investigators at the University of Minnesota include the following: a) the development and implementation of groupwide studies; b) pilot new approaches for the diagnosis and treatment of childhood leukemia and solid tumors which can later be applied on a larger scale in group cooperative studies; c) evaluation of new agents for the treatment of patients with refractory malignancies; d) extension of the studies of bone marrow transplantation for the treatment of hematologic malignancies; e) evaluation of the acute and chronic effects of therapy on vital organ systems; f) development and implementation of new studies of the Intergroup Ewing's Sarcoma Study Committee.

BIBLIOGRAPHIC REFERENCES: Tefft, M., Razek, A., Perez, C., Burgert, E.O., Gehan, E.A., Griffin, P., Kissane, J., Vietti, T., and Nesbit, M.: Local Control and Survival Related to Radiation Dose and Volume and to Chemotherapy in Non-Metastatic Ewing's Sarcoma of Pelvic Bones. Internat. J. Rad. Onc., In press, 1978. Ramsay, N.K.C., Brown, D.M., Nesbit, M.E., Coccia, P.F., Krivit, W. and Krutzik, S.: Autonomous Production of the Parathyroid Hormone by Lymphoblastic Leukemia Cells in Culture. J. Pediatrics. In press, 1978.

342. CHILDREN'S CANCER STUDY GROUP

Leikin, S. L., Reaman, G., Movassaghi, N., Randolph, J. G., Children's Hospital National Medical Center, *111 Michigan Ave. N.W., Washington, District of Columbia,* 20010, United States of America

Our research objective is to pursue our investigations of leukemia and malignant tumor therapy by participation in Children's Cancer Study Group (CCSG). This organization is composed of pediatric hematologists/oncologists, radiotherapists, surgeons, and pathologists from a number of pediatric and cancer institutions, and is involved in protocol studies of pediatric malignancy as formulated by the members of the group. The investigations include the chemotherapy, radiotherapy and immunotherapy trials in acute childhood leukemia and drug therapy trials in solid tumors of the young in conjunction with surgery and radiotherapy. Data on the natural history, complications of treatment and the survival of these patients are collected on an ongoing basis. Statistical supervision is maintained in all of the protocol studies, and in most cases these studies are randomized to prevent bias.

343. CHILDREN'S CANCER STUDY GROUP

Miller, D. R., Steinherz, P. G., Allen, J. C., Tan, C., Memorial Hospital for Cancer & Allied Diseases, Dept. of Pediatrics, *1275 York Ave., New York, New York,* 10021, United States of America

The Children's Cancer Study Group is a multidisciplinary cooperative group of investigators from 26 institutions in the United States and Canada collaborating in the development, implementation and completion of prospective, randomized clinical trials in pediatric hematologic malignancies and solid tumors, including acute lymphoblastic leukemia (ALL), acute nonlymphoblastic leukemia (ANLL), brain tumors, lymphomas (non-Hodgkin's and Hodgkin's), Wilms' tumor, neuroblastoma, rhabdomyosarcoma, bone tumors, hepatoblastoma, 'histiocytosis X', and retinoblastoma. Natural history, biologic characterization of cancer (pathology, immunology, biochemistry), prognostic factors, late effects and supportive care aspects are also stressed in these studies involving pediatric oncohematologists, surgeons, pathologists, diagnostic and therapeutic radiologists, neurologists, psychiatrists, psychologists, cell biologists, immunologists, and infectious disease specialists. New agent Phase II trials for patients failing initial therapy and new modalities of therapy including bone marrow transplantation, are additional major thrusts of the cooperative group. MSKCC - NYH-CMC (and its affiliates) has been a major contributor to the efforts of the Group. This research proposal outlines the center's participation in present and future CCSG endeavors at the executive level as well as in the development of new pilot studies for eventual groupwide participation.

BIBLIOGRAPHIC REFERENCES: Bestak, M., Miller, D.R. and Mouradian, J. : Neurofibromatosis, juvenile chronic granulocytic leukemia and dermal histiocytosis. Amer. J. Dis. Child, 133:831-833, 1979. Luban, N.L.C., Mouradian, J. and Miller, D.R.: Intestinal perforation during remission of ALL. J. Pediatr. 94:409-410, 1979.

344. CHILDREN'S CANCER STUDY GROUP

Piomelli, S., Sitarz, A. L., Wolff, J. A., Weiner, M., Vora, S., Santulli, T. V., Chang, C. H., Blanc, W. A., Berdron, W. E., Columbia University, College of Physicians & Surgeons, Dept. of Pediatrics, *630 W. 168th St., New York, New York,* 10032, United States of America

The Division of Pediatric Hematology of Babies Hospital (the Pediatric Section of the College of Physicians and Surgeons of Columbia University) has participated in the research activities of Children's Cancer Study Group since 1957. Patients have been and will continue to be entered in the clinical trials of this Group, directed at devising optimal therapy for children's cancer and evaluating biological and natural history factors which are important; a multidisciplinary approach to cancer therapy will be followed, both at the institutional and at a national group level. Children with cancer cared for by members of the Division will be entered in the studies of the Group: they will receive medical care standardized to Group requirements, including all required laboratory and diagnostic investigations; accurate records will be kept and transmitted promptly to Group Headquarters for evaluation. Members of the Division will actively participate in the development of the research strategy of new studies. They will participate in the development of the Group scientific program, development and conduct of protocols for Ewing's sarcoma, retinoblastoma and non-Hodgkin's lymphoma, improved modalities for supportive care and definition of biological aspects of childhood cancer, refinement of Pediatric Surgical Oncology techniques and cost effective imaging technique and coordination of the Group Pathology activities.

The Division of Pediatric Hematology/Oncology will coordinate the clinical care of childhood cancer in the Columbia Medical Community. Related research activities within the Division will be developed and eventually expanded to Group trials. These presently include studies of biochemical markers of malignancy; means to decrease toxicity of chemotherapy; the relationship between nutrition, cancer and chemotherapy; newly developed varicella vaccine and epidemiological aspects of perinatal cancer. The interaction between the clinical activities of the Division of Pediatric Hematology/Oncology and the comprehensive Cancer Center of Columbia University will be further developed.

345. CHILDREN'S CANCER STUDY GROUP

Klemperer, M. R., Segel, G. B., Ettinger, L. J., Putnam, T. C., Emmens, R., Rabinowitz, R., Wood, B., Sahler, O. J., Rubin, P., Anderson, V., University of Rochester, School of Medicine & Dentistry, Dept. of Pediatrics, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

This proposal requests continued support for an established children's cancer program at the University of Rochester Medical Center. The objectives of this program are: (1) Optimal patient care and continual improvement in such care through the utilization of collaborative multidisciplinary protocols of a cooperative cancer study group; (2) the evaluation of new approaches to cancer therapy in such areas as new agent development, immunotherapy and supportive care; (3) the definition of factors which may cause and do effect the course of neoplastic disease; (4) the education of practicing physicians, subspecialists, house officers, medical students, nurses and social workers in the diagnosis, treatment and management of children with cancer; and (5) the participation of the Pediatric Hematology-Oncology Unit in all appropriate programs of the University of Rochester Cancer Center.

BIBLIOGRAPHIC REFERENCES: Nusbacher, J., Rosenfeld, S.I., Leddy, J.P., Klemperer, M.R. and MacPherson, J.L.: The leukokinetic changes and complement activation association with filtration leukophoresis. Experimental Hematology 7(Suppl. 4):24, 1979. Segel, G.B., Kovach, G., and Lichtman, M.A.: Human lymphocyte plasma membrane sodium-potassium activated adenosine triphosphatase: Kinetic characteristics, substrate specificity and effect of phytohemagglutinin. J. Cell. Physiol. 100:109-117, 1979.

346. CHILDREN'S CANCER STUDY GROUP

Chard, R. L., Johnson, F. L., Pendergrass, T. W., Children's Orthopedic Hospital & Medical Center, Division of Hematology/Oncology, *4800 Sand Point Way N.E., Box C-5371, Seattle, Washington,* 98105, United States of America

This proposal is for continuation of research into the natural history, treatment and epidemiology of the statistical conduct, design, collation, and publication of childhood cancer. It will continue to emphasize multimodal aspects of the Children's Cancer Study Group which has realized such excellent results in the past in Wilms' tumors and rhabdomyosarcoma and has now helped in defining acute childhood lymphocytic leukemia as more than one disease entity which requires different treatments for different groups. Also, treatment has been improved in osteogenic sarcoma and Ewing's sarcoma and, though advances are more meager, there have also been statistical improvements in survival of neuroblastoma patients. Childhood nonlymphocytic leukemia patients have also shown improved survival and the Children's Cancer Study Group has now combined in a Groupwide study to compare bone marrow transplantation in first remission to more standard conventional chemotherapy in a controlled fashion.

During the period from November, 1976 to December, 1979, 389 children with childhood cancer were seen at this institution; 182 with leukemia, 148 who were treated on study, 44 who were not on study, and 207 children with solid tumors. We have been a member of the Children's Cancer Study Group since 1959 and strong permanent referral patterns have been established. It is therefore anticipated that the patient load will continue to be stabilized and slightly increased over the next several years. A close working relationship with the adult leukemia center under Dr. E. Donnall Thomas at the Fred Hutchinson Cancer Research Center continues. This includes the exchange of professional personnel on the Fellowship level. Forty-three bone marrow transplantations on children with acute leukemia have been done at this institution from 11/1/76 to 12/1/79. Collaborative studies continue in immunology with the Fred Hutchinson Cancer Research Center, primarily through the efforts of Irwin D. Bernstein, M.D.

BIBLIOGRAPHIC REFERENCES: Bleyer, W.A., Krivit, W., Chard, R.L., Hammond, D.: Phase II study of VM-26 in acute leukemia, neuroblastoma and other refractory childhood malignancies. Cancer Treat. Rep. Vol. 63 6:977-981, 1979. Nesbit, M., Chard, R., Evans, A., Karon, M., Hammond, G.D.: Evaluation of intramuscular versus intravenous administration of L-asparaginase in childhood leukemia. Am. J. Pediatr. Hematology/Oncology Vol. 1, 1:9-13, 1979.

D. MYCOSIS FUNGOIDES GROUP AND OTHER GROUPS

347. SCANDINAVIAN MYCOSIS FUNGOIDES STUDY GROUP

Thomsen, K., Molin, L., Finseninstitutet, Dept. of Dermatology, *49 Strandboulevarden, DK2100 Copenhagen, Denmark*

Scandinavian Mycosis Fungoides Study Group is a cooperative study group including dermatological departments in Denmark, Norway and Sweden. The main purpose of the group is to evaluate new forms of treatment of individual stages of the disease.

The results have been published in 12 articles in the Acta dermato-venereologica.

348. MYCOSIS FUNGOIDES COOPERATIVE GROUP

Kaplan, R. S., Wiernik, P. H., Brenner, D., Lambert, S. I., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

The Mycosis Fungoides Cooperative Group was founded in order to study both the natural history of and various treatment regimens for mycosis fungoides in all stages of the disease. To date, 400 cases of pathologically documented mycosis fungoides have been accrued and follow-up information is current on more than 95% of these patients. All data have been computerized and are in the process of being examined to seek correlations with various demographic, history and physical examination, laboratory and pathologic data. Two randomized studies are also in progress and have accrued 80 patients - one study involves patch testing of cutaneous disease and the other involves chemotherapy of visceral disease. The Baltimore Cancer Research Program has entered four patients onto the latter study. Two patients failed therapy, one patient died from bleomycin pulmonary toxicity, and one patient cleared her peripheral blood of Sezary cells but did not clear her skin. Of the 400 study patients who are being followed, but are not on chemotherapy protocols from the study group, there have been 14 from the BCRP and 9 patients continue to be followed by the BCRP. There are no firm conclusions yet from this study.

349. COOPERATIVE STUDY OF HODGKIN'S DISEASE

Hutchison, G. B., Nickson, J. J., Fuller, L. M., Alison, R., Rappaport, H., Viamonte, M., Lee, B. J., Shalek, R. J., Rosenberg, S. A., Kaplan, H., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

Four hundred sixty patients with Hodgkin's disease stages I and II who were enrolled during the years 1967 to 1973 in a collaborative clinical trial comparing involved and extended field radiotherapy will be followed to determine mortality and morbidity through 15 years following enrollment.

Outome measures include survival, extension of disease, and incidence of leukemia and other second primary malignancies.

Initial descriptive variables include age, sex, histologic type, use of diagnostic laparotomy, stage, systemic symptoms.

Continued follow-up will serve to refine outcome measures at the intervals of 5 to 10 years since enrollment and to obtain new measures of outcome at 10 to 15 years. Treatment effects significantly different from zero have been seen in frequencies of extensions and complications but not in frequency of distant extensions or in mortality up to the present date. It is desired to determine whether effects follow this same pattern in later follow-up years or whether early extensions serve as predictors of later distant extensions or death. Five cases of second primary leukemia have occurred, all in patients who had required chemotherapy for extension after radiotherapy.

Twenty institutions have collaborated, and at least one survivor remains under follow-up at 19 of these centers. Continued follow-up will be obtained through collaboration between these centers and the coordinating center. A total of 356 patients remain active. It is estimated that 300 patients will survive to 15 years after enrollment.

350. RADIATION THERAPY ONCOLOGY GROUP

Fu, K. K., Phillips, T. L., Luk, K., Hill, D., University of California, San Francisco Campus, School of Medicine, Dept. of Radiation Oncology, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

Support requested in this application is for the ongoing and expanding participation of the Department of Radiation Oncology of the University of California in San Francisco in the activities of the Radiation Therapy Oncology Group. Comprised of three hospitals, Moffitt, Mt. Zion and Franklin, the Department is staffed by eleven full-time faculty members, treating 2000 new patients per year. The Department has participated in the Group since 1972, entering approximately 150 patients into the various Group protocols, pilot studies and registry protocols during the last year. The Principal Investigator is a member of the Head and Neck Committee, Combination Radiotherapy and Chemotherapy Sub-Committee and Hematopoietic Sub-Committee of the Radiation Therapy Oncology Group. The Associate Principal Investigator is Chairman or the Radiobiology Committee and a member of the Publication Committee, Experimental Design Committee, Lung Sub-Committee, Metastases Sub-Committee, Radiation Injury Sub-Committee, Hyperthermia Sub-Committee and Chairman of the Radiosensitizer/Protector Committee and all staff members serve on the working parties. The group has produced protocols for head and neck cancer, non-Hodgkin's lymphoma, brain metastasis, and hypoxic cell sensitizers, as well as providing input into other protocols. Support through this application will allow RTOG participation by the entire Department and its affiliated institution, the University of California, San Diego, Division of Radiation Oncology and increase the case accession rate to 175-200 new patients per year into the various RTOG protocols. Extensive continuing research into chemical and thermic modification of radiation effects and high LET radiotherapy is expected to lead to innovative protocols and correspondingly to increased accession of patients into studies sponsored by the RTOG.

VI. BROAD PROGRAMS

A. LYMPHOMA-LEUKEMIA AND LEUKEMIA PROGRAMS

351. LYMPHOMA-LEUKEMIA PROGRAM/LAC-USC CANCER CENTER

Lukes, R. J., University of Southern California, School of Medicine, Dept. of Pathology, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

The Lymphoma-Leukemia Program is a unified multidisciplinary study of malignant lymphomas and related leukemias and immunoproliferative disorders that has as its goal the definition of their cellular and clinical characteristics in terms of modern understanding of immunology, including the T and B lymphocytic systems and alterations of lymphocyte transformation. It combines a multiparameter approach employing a variety of immunologic surface marker technics with cytochemistry, ultrastructural, in vitro and immunoglobulin detecting technics for the cellular definition and with in-depth Hodgkin's staging technics for the defining of clinical expressions. The results of the initial definitional phase during the first two years have demonstrated the effectiveness of this multiparameter definitional approach in characterizing human lymphoid neoplasms according to the T and B cell systems and relating these neoplasms to abnormalities of lymphocyte transformation and to the functional lymphoma classification of Lukes and Collins. A Southern California Lymphoma Group involving 28 major area hospitals also has been developed, as part of the regional collaboration to enhance the collection of fresh lymphoma case material for study. It also extends to the community the morphologic, technical and clinical expertise that influences the quality of patient care. This program interrelates with regional epidemiologic and cancer control programs. In the renewal phase of the program the definitional phase will be continued as a basis for in depth areas of investigation that have evolved out of the initial phase. These involve the following areas: IV. Control Mechanisms in Lymphoma Induction and Progression; V. Membrane and Cytoplasmic Immunoperoxidase; VI. Exploratory Data Analysis; VII. Animal Models; VIII. Cell Surface Receptors and Antigens; IX. Cell Kinetics; X. Cytogenetics; XI. Role of Stromal Cells; XII. HLA and B Cell Typing; XIII. Epidemiology.

BIBLIOGRAPHIC REFERENCES: Parker, J.W., Taylor, C.R., Pattengale, P., Royston, I., Tindle, B.H., Cain, M.J., and Lukes, R.J.: A morphological and cytochemical comparison of human T and B lymphoblastoid cell lines: light and electron microscopy. J. Natl. Cancer Inst. 60:59-68, 1978. Lukes, R.J., Taylor, C.R., Parker, J.W., Lincoln, T.L., Pattengale, P.K., and Tindle, B.H.: A morphologic and immunologic surface marker study of 299 cases of non-Hodgkin's lymphomas and related leukemias. Am. J. Pathol. 90:461-486, 1978.

352. LEUKEMIA - LYMPHOMA PROGRAM

Balcerzak, S. P., Whisler, R., Rinehart, J. J., Grever,. M. G., Sagone, A. L., Olsen, R., Hoover, E., Malspeis, L., Schaller, J., Leir, C., Unverferth, D., Schaal, S., Ohio State University, Columbus Campus, School of Medicine, Dept. of Medicine, *370 W. 9th Ave., Columbus, Ohio*, 43212, United States of America

The overall objective of this program is to provide more effective therapy for patients with leukemia and lymphoma. Research will be conducted in two areas - immunology and chemotherapy. Immunologic studies will characterize further the immune defects in patients with untreated lymphoma, determine the effects of therapy on the immune system of these patients and employ an animal model of lymphoma to evaluate immunotherapy as an adjunct to chemotherapy. Chemotherapy studies will focus on adriamycin. Radiolabeled drugs will be used to study the pharmacokinetics of adriamycin and its metabolites. Adriamycin cardiotoxicity will be described in terms of structure, biochemistry and function in animal models and in man. Agents to ameliorate or treat adriamycin cardiomyopathy will be investigated.

353. CLINICAL CANCER RESEARCH PROGRAM

Laszlo, J., Seigler, H. F., Huang, A. T., Paulson, D., Metzgar, R., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina*, 27710, United States of America

This program project renewal application seeks support for multidisciplinary clinical research projects dealing with proposals for new methods of diagnosis and treatment of cancer. The leukemia-lymphoma program has projects in autologous bone marrow transplantation, childhood ALL, studies of newly described morphologic particles, research on lymphoproliferative and myeloproliferative disorders, leukemia immunology, platelet antigens, and biochemical pharmacologic studies of new lipid soluble folate antagonists. Additional programs are described in urologic oncology, which include a range of projects from ultrastructure, culture of human cells and clinical chemotherapy through to metabolic studies of new findings of tumor induced osteomalacia, and prognostic factors in prostatic cancer. Interdisciplinary programs in lung cancer, head and neck cancer, breast cancer, malignant melanoma, and brain tumors are also presented in this application.

The central feature of this request is that we have a newly constructed facility in which multidisciplinary research can be conducted and which provides the optimal conditions for education and patient care and enables the collection of research materials for laboratory investigations. The clinical faculty has been greatly expanded and the scope of research increased accordingly.

354. LYMPHOMA-LEUKEMIA PROGRAM CORE FACILITIES

Ultmann, J. E., University of Chicago, Pritzker School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

This is part of a broader project. A summary of this subproject is not available.

355. LEUKEMIA PROGRAM PROJECT

Simone, J. V., St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

The ultimate objective of this program is to cure children suffering from leukemia. The program is a coordinated effort of therapy and study which includes therapeutic trials aimed at prolonging leukemia-free survival with the more efficient use of conventional agents and the development of new agents, studies of the biology and pathogenesis of leukemia and studies of the effects of leukemia and its therapy on normal tissues.

The program consists of seven interrelated projects: (1) Primary therapy of acute lymphocytic leukemia. (2) Primary therapy of acute non-lymphocytic leukemia. (3) Therapy of relapse of leukemia. (4) Leukemia cell kinetics. (5) Studies of in vitro growth of normal and leukemic marrow. (6) Pathogenesis and therapy of pneumonia. (7) Pathogenesis of pancytopenia in mice.

All projects have the same ultimate objective and, though a wide variety of disciplines are involved, the organization structure provides the means for a unified, coordinated effort.

BIBLIOGRAPHIC REFERENCES: Aur, R.J.A., Simone, J.V., Verzosa, M.S., Hustu, H.O., Barker, L.F., Pinkel, D.P., Rivera, G., Dahl, G.V., Wood, A., Stagner, S., and Mason, C.: Childhood acute lymphocytic leukemia. Study VIII. Cancer 42:2123-2134, 1978. George, S.L., Aur, R.J.A., Mauer, A.M., and Simone, J.V.: A reappraisal of the results of stopping therapy in childhood leukemia. NEMB 300: 269-273, 1979.

356. ACUTE LYMPHOBLASTIC LEUKEMIA (HUMAN)

Sallen, S. E., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

357. CLINICAL ACUTE MYELOGENOUS LEUKEMIA

Rosenthal, D. S., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

358. ACUTE LEUKEMIA (HUMAN)

Gale, R. P., University of California, Los Angeles Campus, School of Medicine, Dept. of Microbiology & Immunology, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

B. LYMPHOMAS AND OTHER COMPREHENSIVE PROGRAMS

359. DEVELOPMENT OF HEALTH STATUS INDICATORS FOR PATIENTS WITH MALIGNANT LYMPHOMA

Till, J. E., Boyd, N. B., Ciampi, A., Bean, H., Ontario Cancer Inst., Division of Biological Research, *500 Sherbourne St., Toronto, Ontario*, M4X 1K9, Canada

OBJECTIVE: To develop a series of validated and reproducible outcome variables that can be used, either singly or in conjunction, in addition to survival or disease response rates, to assess therapy. These variables will permit the comparison of treatments with respect to their ability to relieve or contribute to symptoms, functional disturbance, and distress associated with cancer.

APPROACH: Scales for the classification of functional status, including physical function and psychosocial function, will be developed, using a modification of the approach described by Bush et al. (Health Services Research 11: 478, 1976). Criteria will also be developed to describe symptom/problem complexes in terms of categories of severity. These scales for the classification of functional status and of symptoms will then be tested in the population of interest. Although the initial application will be to the study of patients with lymphoma, it is expected that scales suitable for patients with lymphoma may also be applicable without major modifications to other patients with malignant disease.

360. THERAPY OF LYMPHOMAS, ACUTE ADULT NON-LYMPHOCYTIC LEUKEMIA AND HEPATOCELLULAR CARCINOMA

Todd, D., Ho, F. C., Khoo, R. K., Tso, S. C., Chan, T. K., Ng, R. P., University of Hong Kong, Queen Mary Hospital, Dept. of Medicine, *Pokfulan Rd., Hong Kong, Hong Kong*

OBJECTIVE: To determine the efficacy of combined chemotherapy and/or radiotherapy in Chinese patients with malignant lymphomas, acute adult non-lymphocytic leukemia and hepatocellular carcinoma.

APPROACH: (a) To compare mainly COPP, MOPP, doxorubicin (Adriamycin)-COP, CVP regimes in treatment of lymphomas. Classification: Rappaport, and more recently with T and B cell markers. Staging: Ann Arbor. (b) To use, in adult patients with acute non-lymphocytic leukemia, cytosine arabinoside (ara-C)/doxorubicin i.e. 5:2 scheme for induction; ara-C/thioguanine for remission-induction and azacytidine for refractory cases. (c) Doxorubicin has been used in 19 patients with inoperable hepatocellular carcinoma. In 10, three or more doses were administered and objective evidence of tumor regression was seen in 3. Survival was statistically improved when compared with controls matched for sex, age, duration of symptoms and tumor staging.

PROGRESS: (a) Some results have been reported in Abstracts, XV, International Congress of Haematology, p. 205, Kyoto, 1976. (c) Preliminary data were presented at the Third Asian Cancer Conference in Manila, September 26-30, 1977.

361. PATHOLOGY CENTER FOR LYMPHOMA CLINICAL STUDIES

Rappaport, H., Kim, H., City of Hope Medical Center, Division of Anatomic Pathology, *1500 E. Duarte Rd., Duarte, California*, 91010, United States of America

It is the objective of this project to maintain a Pathology Reference Center and Repository and eight regional centers for the purpose of rendering diagnostic and research support to cooperative clinical studies pertaining to the therapy of malignant lymphomas. The Pathology Reference Center and the regional centers are headed by pathologists who have specialized in the diagnosis and study of neoplastic diseases of the lymphoreticular system and are making a joint effort to improve and refine the criteria for diagnosis and classification of these neoplastic diseases, thereby assuring the validity of the therapeutic results reported by their colleagues engaged in clinical studies. A number of ancillary research projects are being conducted. They are closely related to the primary aim of this project and supplement the clinical studies of the cooperative oncology groups whose investigative programs are supported by NIH grants.

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362. HODGKIN'S DISEASE

Kaplan, H. S., Stanford University, School of Medicine, Dept. of Radiology, *Stanford, California*, 94305, United States of America

This is part of a broader project. A summary of this subproject is not available.

363. MANAGEMENT OF HODGKIN'S DISEASE

Cassileth, P. A., University of Pennsylvania, School of Medicine, Dept. of Medicine, *36th & Hamilton Walk, Philadelphia, Pennsylvania*, 19174, United States of America

This is part of a broader project. A summary of this subproject is not available.

364. PEDIATRIC ONCOLOGY-HODGKIN'S DISEASE

Tan, C. T., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

365. HODGKIN'S DISEASE AND LYMPHOMAS (HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

366. CLINICAL RESEARCH INTO MALIGNANT LYMPHOMAS - PATHOGENESIS, DIAGNOSTICS AND THERAPY OF THE NON-HODGKIN'S LYMPHOMAS

Nieweg, H. O., Halie, M. R., Bins, M., Houwen, B., Mulder, N. H., Hazenberg, B., Fluks, A., Elema, J., Poppema, S., University Hospital of Groningen, Dept. of Medicine, Div. of Hematology, *Oostersingel 59, 9713 EZ Groningen, Netherlands*

OBJECTIVES: a. General: Improvements in diagnostic methods and therapy in Hodgkin's disease (HD) and non-Hodgkin's lymphomas (NHL). b. Specific: Determination of the several types of NHL according to cell type and cell kinetics. Characterization of each subtype as to the behavior of the malignant cells: cell surface properties, cell growth, circulation and dissemination pattern, disease progress. Investigation of factors influencing the origin of the tumor and the course of the disease: serum factors and hormones, viral and bacterial infections, immunological phenomena, sensitivity to therapy.

APPROACH: Determination of intracellular and cell surface membrane characteristics of tumor cells. Investigation of peripheral blood and bone marrow for the same cells. Study of DNA synthesis patterns and recirculation of labelled cells. Investigation of viral antibodies in serum and viral antigens in or on cells. Effects of selective decontamination of the gut on the course of the disease and on the effects of chemotherapy. Techniques: Intracellular and cell membrane marker techniques on sections and cell suspensions; fluorescence and electron microscopy; cytophotometry; autoradiography; isotope labelling of cells; immunochemistry; virus cultures; and microbiological studies.

PROGRESS: Techniques have been developed for characterization of tumor cell types (Rappaport's classification vs. Lukes and Lennert's). Enzyme histochemical studies have revealed the existence of an alkaline phosphatase positive lymphoma. Cell properties of CLL and hairy cell leukemia have been studied in vitro. HCL cells proved to have a cell membrane fluorescence with an anti-muramidase antiserum. Cell circulation studies have been done in CLL and HCL. In the peripheral blood of NHL patients more often than suspected the presence of abnormal cells can be shown either by extensive morphological methods and/or membrane marker studies. EBV and CMV serum antibodies are elevated in patients with CLL and in some with NHL-types.

367. STUDY AND TREATMENT OF CANCER IN THE YOUNG

Levine, A. S., Poplack, D. G., Glaubiger, D., Pizzo, P. A., Deisseroth, A. B., Magrath, I. T., Simon, R., Ziegler, J. L., Rosenberg, S. A., Glatstein, E., Chabner, B., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Pediatric Oncology Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Acute leukemia, non-Hodgkin's lymphomas (e.g., Burkitt's), neuroblastoma, rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma and aplastic anemia are studied. In the treatment of leukemia, we have devised therapeutic regimens which may allow maximum tumor cell kill while minimizing sequellae. Emphasis is on tailoring treatment to individual prognostic variables, and improving the therapeutic ratio in CNS prophylaxis. In treating the solid tumors, we have developed combined modality approaches to primary disease. In refractory tumors, we are studying the utility of high-dose therapy and the role of supportive care (platelet and white cell transfusion, laminar-flow protection, autologous bone marrow rescue, total parenteral nutrition) in permitting such therapy. Phase I-II trails are also conducted in refractory tumors; agents include ICRF-187, poly I:C/poly-l-lysine, dihydroxyanthracenedione, and 2'-deoxycoformycin. We are exploring the biology of selected tumors, including kinetics, immunology, virology, tumor markers, genetics, biochemistry, and pharmacology. Also studied are the effects of cancer and its treatment on growth, development, and organ function. The psychosocial concomitants of cancer are explored.

BIBLIOGRAPHIC REFERENCES: Glaubiger, D., Makuch, R., Schwarz, J., Levine, A.S., and Johnson, R.E.: Determination of prognostic factors and their influence on therapeutic results in patients with Ewing's sarcoma. Cancer 45: 2213-2219, 1980. Shackney, S.E., Bunn, P.A., Ford, S.S., Erickson, B., Ross, W.E., and Levine, A.S.: A study of drug induced kinetic perturbations in the marrow of a patient with neuroblastoma. Cancer 45: 882-892, 1980.

368. NON-HODGKIN'S LYMPHOMA

Rosenberg, S. A., Stanford University, School of Medicine, Dept. of Radiology, *Stanford, California*, 94305, United States of America

This is part of a broader project. A summary of this subproject is not available.

369. COMBINATION THERAPY OF LYMPHOMAS AND SOLID TUMORS (HUMAN)

Githens, J. H., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Medicine, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

This is part of a broader project. A summary of this subproject is not available.

370. AUTOLOGOUS BONE MARROW RECONSTITUTION AND EXTENDED CHEMOTHERAPY IN HUMAN CANCER

Epstein, R. B., Sarpel, S. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *820 S. Damen Ave., Chicago, Illinois*, 60612, United States of America

The present proposal is directed at initiating a pilot trial of the use of cryopreserved autologous hematopoietic stem cells for reinfusion following intensive chemotherapy for the treatment of human neoplasms. Patients selected for the study will include: a) Adults with acute myelogenous leukemia during their first remission following standard chemotherapeutic regimens, b) patients with chronic granulocytic leukemia during the early phase of control, c) patients with small cell and inoperable large cell carcinoma of the lung clinically limited to areas above the diaphragm, d) selected patients with other solid tumors with no demonstrable evidence of bone marrow involvement who fail to respond to a standard chemotherapeutic regimen. Hematopoietic cells will be procured by the multiple marrow aspiration technique under general or spinal anesthesia. Quantities for infusion should exeeed 2 x 10 to the eighth power per kg of body weight. If these numbers are not reached, supplemental peripheral blood hematopoietic stem cells will be obtained by leukapheresis techniques. Cryopreservation of procured cells will be carried out using dimethyl sulfoxide as the cryopreservative and a programmed freezing rate. At the onset of initial leukemic or visceral tumor relapse, intensive chemotherapy protocols will be initiated followed by the infusion of the cryopreserved marrow. Patients will be evaluated in terms of the ability of infused marrow to provide for prompt hematopoietic recovery and for measurable tumor responses. In addition, in vitro assays of granulocyte colony forming units will be performed serially to measure the potential of the assay in monitoring the effect of autologous reinfusion.

371. STUDIES ON CANCER PATIENT DATA CONTROL

Prentice, R. L., Thompson, D. J., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This proposal is to continue the creation and utilization of a patient database, on approximately 2400 patients per year, for the Fred Hutchinson Cancer Research Center. The patient population consists of in-house leukemia patients, patients enrolled in designated Oncology Units in six affiliated hospitals and cancer patients at Children's Orthopedic Hospital. Uniform data on all patients (the minimal data set), along with annual follow-up data, will continue to be pooled with that from other comprehensive cancer centers as part of the SAQC-CCPDS system. The minimal data will hopefully act as a springboard for collaborative research activities during this proposed project period. Data utilization objectives include the analysis of locally generated protocol studies, participation in and analysis of special studies on bone marrow transplant recipients, the production of interim accrual and survival reports to participating Oncology Units and the comparison of survival data on patients in the local SEER (Surveillance, Epidemiology and End Results) and CCPDS databases.

BIBLIOGRAPHIC REFERENCES: Prentice, R.L. (1978). Regression Analysis of Censored Survival Data with Extensions to Include Competing Risks and Case-Control Studies. The Evaluation of Environmental Biological Hazards and Competing Risks. (Ed. Peter Groer). In press.

372. PEDIATRIC ONCOLOGY PROGRAM PROJECT

Krivit, W., Kersey, J. H., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Pediatrics, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The Pediatric Oncology Program Project is an integrated grant covering clinical and preclinical studies in oncology and bone marrow transplantation. A major emphasis of this grant is related to therapeutic investigations with emphasis on marrow transplantation for the treatment of acute leukemia, non-Hodgkin's lymphoma, neuroblastoma, aplastic anemia, and for patients at high risk for kidney graft rejection. Children and adults will be treated in these studies. Emphasis is on total lymphoid irradiation and T-cell depletion of donor bone marrow to reduce the risk of development of graft versus host disease. Preclinical investigations form a major portion of this grant, complementing and interdigitating with the therapeutic studies. Included are investigations into the nature and function of committed hematopoietic marrow cells, platelet pathophysiology, cyclophosphamide metabolism, and adrenergic mechanisms in neuroblastoma. Studies of the etiology of childhood cancers will include evaluation of the role of DNA repair mechanisms and tumor viruses.

373. CANCER CHEMOTHERAPY OF HEMATOLOGIC MALIGNANCIES

Saiers, J. H., Saiki, J., Hardy, W. R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology & Oncology Section, *2100 Ridgecrest Dr. S.E., Albuquerque, New Mexico*, 87108, United States of America

PURPOSE: To evaluate chemotherapy and chemo-immunotherapy regimens in the treatment of human malignancies.

MATERIALS AND METHODS: Patients were treated according to tumor type on various protocols of the Southwest Oncology Group. Currently, there are 42 active protocols being used at this institution. In the past year, 22 patients have been registered on protocols.

RESULT: Four patients with malignant lymphomas were treated. Three achieved complete response and remain in complete remission. One achieved a partial response and has since relapsed. Two patients with malignant melanoma were treated. One had a complete response, but then refused further therapy until he had recurrence of his disease. Three patients suffering from malignancies of the bladder (1), salivary gland (1), lung (1) were treated and all achieved partial responses. One patient each with acute leukemia, malignancy of prostate, head and neck malignancy were treated and had no responses. A number of patients have been treated on Phase II studies including 4 lung, 2 melanoma, 1 each myeloma and lymphoma colon, and acute leukemia and none of these patients have responded to therapy. There has been no untoward toxicity during the past 12 months in any of our patients and we will continue to place as many patients on protocol as possible.

374. HUMAN HEMATOPOIETIC TUMORS PROGRAM PROJECT GRANT

Clarkson, B. D., Moore, M. A., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

There is still considerable uncertainty about the accurate classification of human hematopoietic tumors, as well as considerable variability in prognosis and in response to treatment, not only among different hematopoietic tumors, but also within any one diagnostic category. More precise diagnosis and definition of the relationships between these tumors is therefore important, not only in terms of reaching a clearer understanding of their cellular origins, but also in predicting prognosis, evaluating current treatment regimens, and developing more effective methods of therapy.

The main purpose of this Program Project is to carry out a comprehensive clinical laboratory investigation of all varieties of hematopoietic tumors, with emphasis on correlating the results of newer laboratory studies which have potential clinical relevance with conventional hematological and pathological diagnostic criteria, and with clinical data on staging, responsiveness to treatment and survival. The investigations include determination of surface and biochemical markers, receptors, cytokinetic parameters, size distribution, clonogenic potential in short-term culture systems, response to mitogens, interactions with other cell types in culture, establishment of human tumor cell lines, ultrastructural cytology, cytogenetics, and DNA and RNA histograms.

The eventual goal is to help develop an objective and scientific classification system for human hematopoietic tumors based on the origins and functional properties of the cells. Once an accurate classification system has been formulated which will permit us to reliably identify the critical prognostic factors at the time of diagnosis, it should be possible to plan more rational and appropriate treatment programs for the hematopoietic tumors.

375. MYELOPROLIFERATIVE DISORDERS (HUMAN)

Schrier, S. L., Stanford University, School of Medicine, Dept. of Medicine, *Stanford, California*, 94305, United States of America

This is part of a broader project. A summary of this subproject is not available.

INVESTIGATOR INDEX

Aardal, N.P. 101
Addison, I.E. 183
Aherne, G.W. 77, 102
Aine, R. 207
Aisenberg, A.C. 172, 192
Aisner, J. 76, 99, 290
Al Atar, A. 226
Alavaikko, M. 207
Alimena, G. 145
Alison, R. 349
Allen, J.C. 343
Amadori, S. 145
Anderson, B. 118
Anderson, H.R. 40
Anderson, V. 345
Andreeff, M. 21
Antia, P.K. 33
Appelbaum, F.R. 72, 85, 261
Arlin, Z.A. 75
Askergren, J.N. 154
Aufses, A.H. 310
Aur, R.J. 40, 137
Avanzi, G. 267, 277
Babbage, J. 183
Baccarani, M. 14, 61, 80
Bach, P.B. 335
Bachand, A. 172, 192
Bacharach, S.L. 165
Bacigalupo, A.P. 267, 277
Bakay, B. 89
Baker, D.C. 107
Balcerzak, S.P. 352
Baldini, L. 110
Balkwill, F. 124
Ballard, H. 144, 206
Ballard, H.S. 320
Banfi, A. 166, 178
Barboni, F. 263
Barone, R. 304
Barrett, A.J. 260
Barthel, B. 103
Bartoli Klugman, F. 110
Bashir, H. 262, 276
Bassoe, C.F. 101
Bast, R.C. 120
Bean, H. 359
Beck, E.A. 273
Begent, R.H. 156
Bell, P.A. 9
Bell, R. 78, 139, 225, 239
Beltrandi, E. 263
Bensinger, W. 275
Benzel, J. 305
Beran, M. 118
Berdron, W.E. 344
Berenberg, J.L. 297
Berkowitz, I.M. 305
Bernard, J. 303
Bertoli, G. 110
Bias, W. 18
Biasi, 166, 178
Biggs, J.C. 262, 276
Bilek, F. 242
Bins, M. 366
Bistolfi, F. 267, 277
Bjorkholm, M. 154
Blanc, W.A. 344
Blaylock, W.K. 258
Bleyer, W.A. 112
Blom, J. 297
Bloomfield, C.D. 189, 231, 298
Blum, R.H. 144, 206
Bodwell, J. 307
Boggs, S.S. 114, 269
Boivin, J. 172, 192
Boivin, J.F. 181
Bonesana, A.C. 241
Borer, J.S. 165
Bostick, F. 187
Bottomley, R.H. 149, 150, 151, 152, 203, 247, 286
Boyd, N.B. 359
Bradley, J. 26
Branda, R.F. 30
Brandt, L. 254
Brearley, R.L. 78, 225
Breitman, T. 76
Brenner, D. 76, 348
Brigham, K.L. 287
Brody, R.S. 167, 182
Brown, T. 174, 191
Brox, L.W. 65
Broxmeyer, H.E. 23
Buchanan, J.G. 249
Bucher, U. 273
Buckner, C.D. 72, 85, 261, 275, 289
Bunn, P.A. 204, 242, 243
Buraggi, 166, 178
Burchenal, J.H. 97
Burgert, E.O. 94
Burghouts, J. 19
Burgoyne, 26
Burke, P.J. 134
Burlington, H. 59
Byfield, J. 304
Camacho, A. 200
Camitta, B.M. 42
Cangir, A. 332
Cant, 26
Carbone, P. 230
Carey, R.W. 296
Carpenter, J.T. 116
Carrillo, J. 141
Carsten, A.L. 59
Casalone, R. 13
Casper, J.T. 132
Cassileth, P.A. 363
Catovsky, D. 64
Cavallo, V. 159, 211
Chabner, B. 367
Chan, T.K. 360
Chanana, A.D. 59
Chang, C.H. 344
Chard, R.L. 112, 346
Chechik, B.E. 7
Cheever, M.A. 72, 85, 261
Chester, K. 156
Chien, L. 40
Ciampi, A. 359
Clark, A.M. 26
Clarkson, B.D. 75, 109, 374
Clift, R.A. 289
Cline, M.J. 3
Coccia, P.F. 341
Cohen, H.J. 127
Cohen, M.H. 204, 243
Colbert, M. 315
Coltman, C.A. 325, 326, 327, 328, 329
Comis, R.L. 301
Concannon, J.P. 331
Cooper, I.A. 184, 233
Cooper, M.D. 336
Copper, M.R. 311
Corley, C.C. 323
Cornwell, G.G. 302, 307
Cortellaro, M. 143, 244
Cox, 26
Cox, E. 324
Craddock, P.R. 287
Creaven, P. 322
Crist, W.M. 336
Cronkite, E.P. 59
Culbert, S.J. 332
Cullen, M.H. 139, 288
Cupps, R.E. 94
Cuttner, J. 123, 310
D'Antonio, D. 263
Dahl, G.V. 32
Dahl, T. 5, 38
Daling, J.J. 17
Dalmasso, A.P. 287
Damie, S.R. 33
Darrell, J. 64
David, V. 159, 211
Davies, R.E. 235
De Felice, L. 145
Dearth, J.C. 336
Deisseroth, A.B. 367
deKoning, J. 44, 268
Delamore, I. 117
DelDuca, V. 305
Delmonte, L. 109
Demian, S. 216
Desforges, J.F. 172, 192
DeSousa, M. 23
Dessypris, E. 68
Di Bartolomeo, P. 263
Di Girolamo, G. 263
Di Lorenzo, A. 145
Diez, R. 84, 188, 228
Ding, J.C. 184, 233
Djerassi, I. 143, 244
Donoso, J. 10
Dooley, T. 106
Dooren, L.J. 44, 268
Douglass, H.O. 322
Dow, L.W. 133
Downey, A. 144, 206
Draper, G.J. 28
Drenthe Schonk, A. 93
Dritschilo, A. 316
Drucker, W.D. 42
Duck, S.C. 42
Duffy, P. 76
Duhamel, G. 265
Dukkers van Emden, D. 185
Dunleavy, S. 144, 206
Dunnick, N.R. 214

Dutcher, J.P. 290
Egan, J. 305
Einstein, A. 201
Ekert, H. 31, 35, 283, 291
Elema, J. 366
Ellis, W.M. 283
Emmons, R. 345
EppingerHelft, M. 148
Epstein, J. 60
Epstein, R.B. 370
Esterhay, R.J. 81
Estevez, M.E. 84, 188, 228
Ettinger, L.J. 345
Evans, A.S. 163
Evert, C.F. 46
Ezdinli, E.Z. 321
Falcetti, E. 274
Fay, J. 324
Fay, J.W. 270
Fefer, A. 72, 85, 261
Flaiasz, M. 84, 188, 228
Finklestein, J.Z. 340
Finlay Jones, 26
Floritoni, G. 263
Fischer, J.J. 155
Fischmann, B.A. 242
Fisher, R.I. 187, 204, 243
Flexner, J.M. 58
Fluke, A. 366
Ford, J.M. 78, 239, 288
Forman, J. 216
Fortner, C.L. 74
Fraass, B.A. 221
Fraccaro, M. 13
Francis, G.E. 62
Frankel, L.S. 332
Frappier Davignon, L. 119
Freeman, A.I. 142, 337
Freeman, C.B. 117
Frei, E. 66, 83
Freireich, E.J. 334
Frelick, R.W. 305
Frenkel, E.P. 216
Frenning, D. 298
Frich, J.C. 317
Fridland, A. 108
Fried, J. 75, 109
Frizzera, G. 189, 231
Fu, K.K. 350
Fuller, L.M. 349
Fust, G. 284
Gahrton, G. 16
Gajl Peczalska, K.J. 189, 231
Gale, R.P. 358
Galli, M.C. 71, 88
Gandossini, M. 183
Garavaglia, G. 115
Garcia, I. 200
Garson, O.M. 184, 233
Gentile, T. 8
George, S. 40
Geraci, L. 263
Gerken, M. 315
Ghilezan, N.I. 253
Gilchrist, G.S. 94
Giraldi, T. 110
Githens, J.H. 369
Glatstein, E. 169, 180, 221, 367
Glaubiger, D. 367
Glicksman, A. 315
Glidewell, O.J. 299
Gobbi, M. 61, 71, 80, 88
Goff, J.R. 40
Goldman, A. 189, 231
Golombe, B. 341
Gonzalez, E. 285
GordonSmith, E.C. 259
Gorin, N.C. 265
Gottdiener, J.S. 165
Gottlieb, A.J. 301
Graber, S.E. 68
Gracz, K. 321
Gratwohl, A. 266
Greaves, M.F. 78
Grebe, G. 10
Greco, F.A. 58
Green, M.V. 165
Greenberg, P.D. 72, 85, 261
Greenberg, P.L. 126
Greene, M. 187
Greipp, P.R. 94
Grever, M.G. 352
Griffin, T. 222, 232
Grifoni, V. 197
Groudine, M. 222, 232
Grove, W.R. 74
Grozea, P. 203, 247
Grozea, P.N. 149, 150, 151, 152
Gunzing, A.R. 42
Guerris, R. 159, 211
Gugliotta, L. 14
Guindani, 166, 178
Guintoli, J. 84, 188, 228
Gunz, F.W. 1, 12, 100
Gutensohn, N. 163
Hannon, C. 19, 93
Hagen, T.C. 42
Hajdu, S.I. 167, 182
Haley, C.L. 333
Halie, M.R. 366
Hamilton, L. 144, 206, 320
Hanker, J.S. 4
Hansen, H. 109
Hansen, H.J. 75
Hardy, W.R. 373
Harnden, D.G. 28
Harper, R.A. 235
Harris, H.H. 317
Harris, R. 117
Harris, R.A. 259
Hartmann, J.R. 112
Harvey, V. 118
Hast, R. 138
Hathaway, W.E. 312
Haurani, F.I. 107
Hawkins, L.D. 366
Hazenberg, B. 28
Heasman, M.A. 323
Heffner, L.T. 3
Heindell, H. 207
Heiln, H. 172, 192
Hellman, S. 45, 122, 136, 300
Henderson, E.S. 317
Hendrick, A.M. 308, 318
Henry, P.H. 12
Hersey, P. 300
Higby, D.J. 3
Higuchi, R. 350
Hill, D. 321
Hindo, W.A. 297
Hirata, R.M. 360
Ho, F.C. 94
Hoagland, H.C. 281
Hoffbrand, A.V. 132
Holcenberg, J.S. 284
[illegible], R. 55, 57, 299, 310
Holland, J.F. 154
Holm, G. 280
Holt, J.D. 352
Hoover, E. 47
Hopewell, J.W. 319
Horton, J. 316
Hoth, D.F. 366
Houwen, B. 298
Hrushesky, W. 353
Huang, A.T.
Hubbard, V.S. 49
Hughes, J. 331
Huguley, C.M. 323
Humphrey, G.B. 53, 236
Humphrey, R. 18
Hurd, D. 298
Hussein, K.K. 149, 150, 151, 152, 203, 247, 286
Hutchison, G.B. 172, 181, 192, 349
Iacone, A. 263
Ihde, D.C. 204, 243
Imonen, R. 297
Ionesco, F. 115
Isacchi, G. 145
Islam, K.M. 199, 245
Ismail, M. 213
Jaffe, E. 187
Jaffe, N. 332
James, G.W. 293
Janossy, G. 281
Jimenez, E. 141, 200
Jimenez, R. 141, 200
Johansen, O.J. 6, 39
Johansson, B. 154
Johnson, F.L. 346
Johnson, G. 290
Johnson, L. 262, 276
Johnson, S.A. 139
Jones, A.E. 177
Jones, B. 314
Jose, D.G. 35
Jovanovic, L. 321
Kane, S. 160
Kaan, S. 315
Kadin, M. 222, 232
Kamphuis, R.P. 44, 268
Kaneko, A. 292
Kang, M.S. 131
Kaplan, H. 349
Kaplan, H.S. 362
Kaplan, R.S. 198, 240, 348
Karbal, A. 47
Karcher, D. 297
Katin, M.J. 165
Katz, L. 48
Kay, H.E. 260
Keen, J. 156, 209
Keighley, 26
Keller, J.W. 323
Keller, R.H. 132
Kellerman, J. 49
Kennedy, B.J. 298
Kersey, J.H. 372
Kettman, J.R. 216
Khaleque, S.A. 199, 245
Khaliq, A. 111, 140, 246
Khoo, R.K. 360
Kiang, D. 298
Kim, H. 361
Kim, T.H. 172, 192, 333
Kimball, D.B. 297
Klemperer, M.R. 345
Klitgaard, H. 42
Knapp, R.C. 120
Knight, M. 305
Knowles, D.M. 217
Koenig, H.M. 335
Koppe, J.G. 185
Kostraba, N. 298
Kotelba Witkoska, B. 290
Koury, M. 68
Kramer, B.S. 186, 229
Krantz, S.B. 68
Krivit, W. 341, 372
Krizan, Z. 187
Kumar, P.P. 242
Kumlien, G. 69
Kummoona, R. 226

Kummoona, R.K. 213
Kung, F.H. 43, 50, 89, 304, 335
Kurnick, J.E. 278
Kyle, A. 305
Kyle, R.A. 94
Laerum, O.D. 101
Lahey, M.E. 338
Lakshmanan, A.V. 158, 176, 212
Lambert, S.I. 348
Lampkin, B.C. 46, 121
Lamy, P.P. 74
Lantz, B. 118
Laszlo, J. 353
Lauer, S.J. 132
Lauria, F. 14
Lavallee, R. 172, 192
Lavergne, B. 119
Leahy, M.A. 34
Lee, B.J. 349
Leikin, S.L. 342
Leir, C. 352
Lenhard, R.E. 256
Lennert, K. 220
Leone, L.A. 315
LePage, G.A. 111, 140, 246
Leventhal, B.G. 313
Leventhal, H. 230
Levin, M. 144, 206
Levine, A.S. 367
Linet, M. 18
Lipson, L.C. 165
Lister, T.A. 78, 139, 225, 239
Loannes, A. 274
Lobo, J.F. 200
Logue, G.L. 127
Long, J. 163
Love, R. 230
Lui, V.K. 333
Luk, K. 350
Lukes, R.J. 351
Ma, D. 262, 276
Macdonald, J.S. 316
MacMahon, B. 163
Maddocks, J.L. 106
Madsen, M. 208
Magrath, I.T. 367
Majhi, U. 215
Malpas, J.S. 78, 139
Malspeis, L. 352
Mandelli, F. 145, 274
Mann, D. 187
Mann, S.J. 235
Maraschio, P. 13
Marini, M. 159, 211
Marks, V. 77, 102
Markus, S. 76, 99
Marmont, A.M. 267, 277
Marsden, H.B. 28
Marten, G.W. 40
Martin, ... 26
Matthews, J. 35
Matthews, J.R. 249
Matthews, R.N. 35
Maurer, L.H. 302, 307
McCredie, K.B. 95, 334
McIntosh, L.S. 86
McIntyre, O.R. 302
McKenna, R.W. 189, 231
McMillan, A. 333
Meenakshi, A. 161, 218
Mellstedt, H. 154
Meloni, G. 274
Mendelson, J. 304
Merigan, T.C. 126, 251, 252
Merritt, W. 132
Methot, Y. 172, 192
Metzgar, R. 353
Meyers, J.D. 125
Meyers, P.A. 23
Minh, M.N. 199, 245
Michael, A. 161, 218
Miles, N.I. 253
Miller, D.R. 343
Miller, D.S. 96
Miller, M. 59
Mills, R. 305
Minna, J.D. 204, 243
Mitchell, B.S. 82
Mitchell, M.S. 67
Mittelman, A. 322
Mod, A. 284
Moe, P.J. 5, 6, 38, 39
Mogut, D.I. 253
Mohan, R. 167, 182
Moldow, C.F. 287
Molin, L. 347
Momparler, R.L. 147
Monti, M. 254
Montuoro, A. 145
Moore, J. 324
Moore, M.A. 374
Moore, M.R. 323
Morgenfeld, M.C. 202, 250
Morild, I. 101
Morley, ... 26
Moss, H.A. 49
Mott, M.G. 8
Movassaghi, N. 342
Muggia, F.M. 144, 206
Muir, P.D. 100
Mulder, N.H. 366
Muller, H. 27
Muller, J.Y. 265
Munck, A. 189, 231
Murphy, J. 107
Murphy, M.L. 29
Murphy, S. 104
Murray, ... 26
Murray, J.L. 149, 150, 151, 152, 203, 247
Muthiah, R. 161, 218
Muzzi, G. 263
Nachman, R.L. 306
Nadkarni, J.S. 33
Nadkarni, K.S. 33
Najman, A. 265
Nanni, P. 71, 88
Nava, H. 322
Navarrete, M. 141
Neefe, J. 316
Neglia, W. 297
Neiman, P. 201, 222, 232
Neiman, P.E. 125
Nerenz, D. 230
Nesbit, M.E. 341
Newman, K.A. 74
Ng, R.P. 360
Nickson, J.J. 349
Nieweg, H.O. 366
Nishiya, N. 23
Nisi, C. 110
Nissen, C. 266
Nixon, D. 323
Noell, T. 324
Nordenskjold, B. 227
Nordentoft, A.M. 160
North, W.G. 307
Nygaard, R. 5, 38
Nyhan, W.L. 89, 304, 335
O'Brien, M.S. 333
O'Donnell, J.F. 302
O'Leary, M. 341
Odavic, R. 273
Olisa, E.G. 162
Olsen, R. 352
Olsson, H. 254
Opheim, K.E. 112
Oser, H. 300
Padikal, T.N. 221
Pagnoni, ... 166, 178
Pallesen, G. 208
Palva, I. 54
Paolucci, P. 130
Papa, G. 145
Papamichael, M. 24
Pasquali, F. 13
Pasqualetti, D. 145
Paul, C. 69
Paulson, D. 353
Pavlovsky, S. 79, 146, 148, 202, 241, 250
Paxton, A.M. 139
Pendergrass, T.W. 41, 346
Penny, R. 262, 276
Periti, P. 143, 244
Peters, G. 185
Petersen, B. 298
Peterson, B.A. 189, 231
Peterson, C.O. 69
Petit, J.C. 265
Petti, M.C. 145
Pfrimmer, W.J. 331
Phillips, L.A. 131
Phillips, T.L. 350
Piall, E. 77, 102
Piccardo, C. 197
Pierri, I. 197
Pilch, Y.H. 304
Piomelli, S. 344
Pizzo, P.A. 367
Polli, E. 143, 244
Poplack, D.G. 49, 367
Poppema, S. 366
Poretti, G.G. 115
Porfiri, L.M. 159, 211
Powazek, M. 40
Powles, R. 260
Preisler, H.D. 56, 300
Prentice, H.G. 281
Prentice, R.L. 371
Presant, C.A. 190
Probert, J.C. 249
Prodi, G. 71, 88
Prosnitz, L. 175, 194
Prosnitz, L.R. 255
Prosser, E.J. 100
Pugh, R.P. 331
Pun, A. 262, 276
Putnam, T.C. 345
Quaglino, D. 219
Rabinowitz, R. 345
Rafla Demetrious, S. 309
Ragab, A.H. 333
Rahim, M.A. 199, 245
Raich, P.C. 317
Rajalakshmi, K.R. 215
Rajalakshmi, P.K. 158, 212
Ramsay, N.K. 341
Randolph, J.G. 342
Rappaport, H. 349, 361
Rapson, N. 130
Reali, G. 267, 277
Reaman, G. 342
Recchione, ... 166, 178
Rege, V. 315
Reichlin, S. 129
Reid, A.M. 167, 182
Reizenstein, P. 118
Ricci, P. 61, 80
Rice, M.S. 34
Ridell, B. 20
Ried, H.L. 332
Rinehart, J.J. 352
Ringler, K. 230
Ritz, J. 120
Rivard, G.E. 147

Rivera, G. ... 52
Roberson, P.L. ... 221
Roberts, M.M. ... 78
Rodari, ... 166, 178
Rodriguez Lopez, E. ... 285
Rogers, J.S. ... 317
Rohatiner, A. ... 124
Roper, M. ... 336
Rosato, V. ... 145
Rosenberg, S.A. ... 252, 349, 367, 368
Rosenthal, D.S. ... 357
Rothbarth, P.H. ... 44, 268
Rowley, J.D. ... 73, 113
Rubin, P. ... 224, 345, 365
Ruggero, D. ... 61, 80, 266
Rundles, R.W. ... 105
Ruymann, F. ... 297
Rybka, W.B. ... 70, 87
Sackmann Muriel, F. ... 79, 146
Safai, B. ... 257
Sagone, A.L. ... 352
Sahler, O.J. ... 345
Saiers, J.H. ... 373
Saiki, J. ... 373
Sako, K. ... 322
Sakurai, M. ... 292
Sallan, S.E. ... 356
Salmon, C. ... 265
Salser, W. ... 3
Salvatore, P. ... 164
Samii, S. ... 305
Sampi, K. ... 292
Sanani, S. ... 98, 171, 173, 179, 193, 196, 294, 295
Sangiuolo, A. ... 197
Santoro, ... 166, 178
Santucci, M. ... 61, 80
Santulli, T.V. ... 344
Sanyal, S. ... 51
Sarin, P. ... 76
Sarpel, S.C. ... 370
Sava, G. ... 110
Scarsi, P.G. ... 197
Schaal, S. ... 352
Schaller, J. ... 352
Schechter, G. ... 242
Schein, P.S. ... 316
Schiffer, C. ... 76
Schiffer, C.A. ... 90, 290
Schiffer, L.M. ... 331
Schilling, A. ... 315
Schimpff, S. ... 76
Schimpff, S.C. ... 74, 164
Schnipper, L. ... 168, 195, 237
Schottenfeld, D. ... 167, 170, 182
Schreiber, A.D. ... 223, 234
Schrier, S.L. ... 135, 375
Schubert, E. ... 305
Schwartz, D.B. ... 335
Schwarz, M. ... 184, 233
Scialla, S. ... 297
Scudeletti, M. ... 197
Segel, G.B. ... 345
Seigler, H.F. ... 324, 353
Sen, L. ... 84, 188, 228
Shahidi, N.T. ... 339
Shalek, R.J. ... 349
Shanta, V. ... 158, 212
Shay, J.W. ... 216
Sheehan, R. ... 216
Sheehan, R.G. ... 91, 205, 248
Sheehan, W. ... 216
Shetty, P.A. ... 33
Shingleton, W. ... 324
Shipman, G. ... 298
Siegel, S. ... 49
Silberman, H.R. ... 324
Silver, R.T. ... 299, 306
Simmons, G. ... 333
Simon, R. ... 367
Simone, J.V. ... 355
Simonsson, B. ... 15
Singer, J. ... 125
Sitarz, A.L. ... 344
Skoog, L. ... 25, 157, 210
Slawson, R. ... 169, 180
Sloman, J.C. ... 9
Smets, L.A. ... 92
Smith, A. ... 249
Smith, C. ... 305
Smith, F.P. ... 316
Smith, K.A. ... 189, 231
Smith, P.J. ... 291
Smith, R.G. ... 216
Smithson, W.A. ... 94
Soothill, J. ... 130
Souhami, R.L. ... 183
Soule, E.H. ... 94
Spaulding, M.B. ... 98, 171, 173, 179, 193, 196, 294, 295
Speck, B. ... 266
Spinelli, ... 166, 178
Stalder, G. ... 27
Stang, H.D. ... 3
Starling, K.A. ... 272
Steenbergen, J. ... 19
Stein, R.S. ... 58
Steinherz, P.G. ... 343
Steinitz, R. ... 48
Stewart, P. ... 275
Storb, R.F. ... 282
Strauss, J.F. ... 91, 205, 248
Subramanian, V.P. ... 317
Sukumaran, M.S. ... 215
Sullivan, K.M. ... 201, 222, 232
Sullivan, M.P. ... 332
Sundblad, R. ... 154
Sutcliffe, S.B. ... 177
Sutow, W.W. ... 332
Swanson, G.M. ... 163
Swolin, B. ... 20
Szklo, M. ... 18
Tabacchi, P.L. ... 263
Taboada, H. ... 10
Tamburlini, V.S. ... 253
Tan, C. ... 343
Tan, C.T. ... 167, 182, 364
Tauro, G.P. ... 35
Tawil, E. ... 172, 192
Terada, M. ... 2, 63
Terasaki, P. ... 290
Terenius, L. ... 15
Testa, M.G. ... 145
Theologides, A. ... 298
Thomas, E.D. ... 72, 85, 125, 261, 264, 271, 275, 279, 289
Thompson, D.J. ... 371
Thomsen, K. ... 347
Thuet, C. ... 172, 192
Till, J.E. ... 359
Timothy, A. ... 177
Todd D. ... 360
Tognella, S. ... 197
Toogood, I. ... 291
Toogood, I.R. ... 34
Torlontano, G. ... 263
Trujillo, J.M. ... 22
Tsiapalis, C.M. ... 24
Tso, S.C. ... 360
Tsuchimochi, T. ... 292
Tucker, D.F. ... 156
Tura, S. ... 61, 80
Udayachander, M. ... 161, 218
Uden, A. ... 118
Uhr, J.W. ... 216
Ultmann, J.E. ... 354
Unverferth, D. ... 352
Urbach, F. ... 235
Utley, J. ... 304
Van Echo, D.A. ... 99, 128
Van Eys, J. ... 332
Van Lint, M.T. ... 267, 277
Van Scott, E.J. ... 235, 238
Van Sloten, K. ... 76
Vanhaelen, C. ... 187
Varcoe, A.R. ... 249
Viamonte, M. ... 349
Vietti, T.J. ... 330
Villani, ... 166, 178
Vincent, P. ... 262, 276
Vincent, P.C. ... 1, 100
Vincent, R. ... 322
Viswanathan, K.S. ... 176
Vitale, V. ... 267, 277
Vitetta, E.S. ... 216
Vitols, S. ... 69
Vogelzang, N. ... 298
Vogler, W.R. ... 323
Vohr, F. ... 315
Volterrani, ... 166, 178
Vonderheid, E.C. ... 235
Vora, S. ... 344
Vosika, G. ... 298
Vossen, J.M. ... 44, 268
Vreeland, F. ... 315
Waddell, C.C. ... 11
Waldenstrom, J. ... 20
Walker, B.K. ... 317
Walker, L.C. ... 209
Wampler, G.L. ... 153
Wasser, L. ... 321
Wasserman, L.R. ... 310
Waters, K.D. ... 31, 35, 283
Watling, D. ... 124
Watne, A.L. ... 317
Watt, J.L. ... 174, 191
Wehinger, H. ... 36, 37
Weiden, P. ... 289
Weiner, M. ... 344
Weiner, R.S. ... 186, 229
Weinfeld, A. ... 20
Weiss, N.S. ... 17
Wernz, J.C. ... 144, 206
Wessels, J. ... 19, 93
Whisler, R. ... 352
White, J.C. ... 287
Whitehead, T. ... 333
Wiernik, P.H. ... 74, 76, 81, 90, 99, 128, 164, 169, 180, 198, 240, 290, 348
Williams, A.O. ... 162
Winton, E.F. ... 323
Wiswell, J.G. ... 164
Wolff, J.A. ... 344
Wong, K.Y. ... 46
Wood, B. ... 345
Woodard, J.R. ... 333
Woodruff, R.D. ... 333
Woodward, K. ... 324
Woolley, P.V. ... 316
Wozniak, T.F. ... 305
Wrigley, P.F. ... 177
Yen, A. ... 109
York, R.M. ... 323
Young, R.C. ... 169, 180
Young, V.M. ... 76
Yu, A.L. ... 89, 304
Zaccaria, A. ... 14
Zacharski, L.R. ... 302
Zbroja, R. ... 1, 100
Zidar, B.L. ... 331
Ziegler, J.L. ... 367
Zola, H. ... 26
Zucali, ... 166, 178
Zucker, S. ... 59
Zahrie, S.R. ... 117

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